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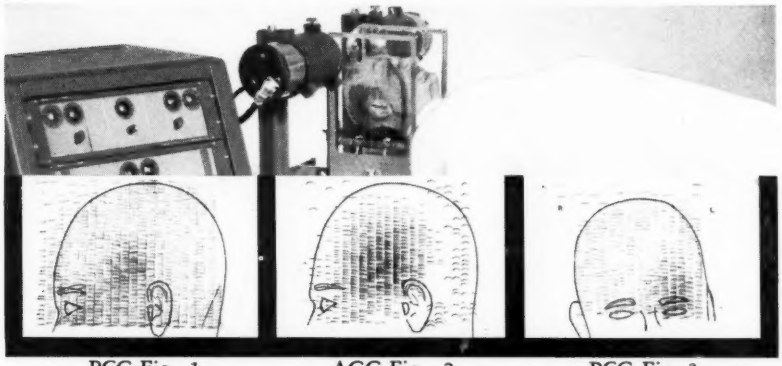

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*Reference: Brownell, G. L. and Sweet, W. H., "Scanning of Positron-Emitting Isotopes in Diagnosis of Intracranial and Other Lesions", Proceedings of the Geneva Conference, Vol. 10, P. 249, 1956.

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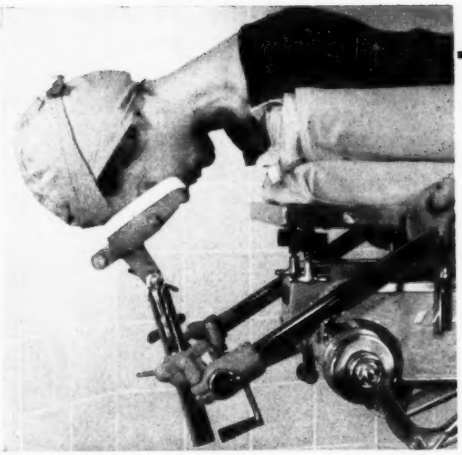

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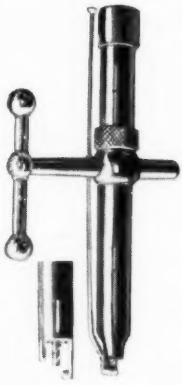

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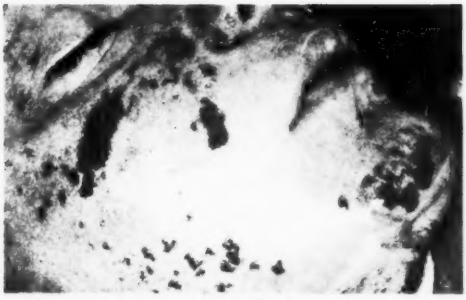

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1. *Dripps, R.D.: Hazards of the Immediate Postoperative Period, J.A.M.A. 7:795 (Oct. 19, 1957) [This reference reviews postoperative hazards, and does not refer to Adrenosem Salicylate]*
2. *Ersner, M.S., and Lerner, S.S.: M. Clin. North America 40:1749 (Nov., 1956)*
3. *Peele, J.C.: Further Observations on the Use of Adrenosem Salicylate in the Control of Hemorrhage from the Nose and Throat, N. Carolina M.J. 17:98 (March, 1956)*
4. *Brown, W.S.: The Use of Adrenosem Salicylate to Control Postoperative Bleeding in Plastic Surgery: Dermabrasion, Northwest Medicine. In Press.*
5. *Wilkins, B.D.: Gastrointestinal Bleeding as Seen by the Proctologist, J.A.M.A. 163:1214 (April 6, 1957)*
6. *Orzac, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy, N.Y. State J. Med. 55:886 (Mar., 1956)*
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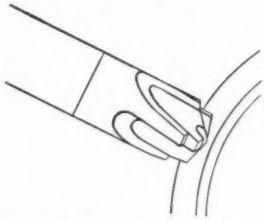

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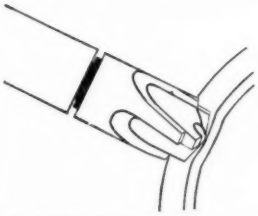

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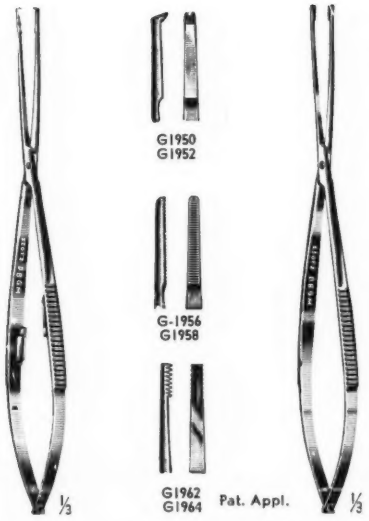

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*Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Co., 1956, p. 505.

IN FAVOR OF SIMPLICITY: APPLIED TO MEDICINE IN GENERAL AND NEUROSURGERY IN PARTICULAR

R. EUSTACE SEMMES, M.D.*
Memphis, Tennessee

(Received for publication July 19, 1957)

MEDICAL care is steadily becoming more complex and more costly. I believe it is time to re-evaluate many of the modern innovations and to determine whether they are as often indicated as they are generally used or as reliable as at first thought.

Diagnostic procedures have multiplied, and although each one may be essential at times, they are time-consuming, painful, expensive, and not without danger. Certainly, we should endeavor to choose the one most likely to turn up with the answer and, at least, to see that the patient runs the gauntlet of the electroencephalogram, pneumoencephalogram, ventriculogram, arteriogram, venogram and isotopic concentration in the most likely order. Myelography for diagnosis of lumbar discs is used routinely by some neurosurgeons, although the clinical picture is far more reliable and every patient who has had both myelography and surgery insists that the myelography is more painful and trying. X-ray films made in various positions, at various angles, and frequently stereoscopically are apt to stack up until they need baling. We seem to get along satisfactorily with a much smaller number of carefully selected views. There is now reason to believe that patients undergoing diagnostic studies can be injured by excessive irradiation. It may be that even the progeny will be damaged for generations to come. Frequently, laboratory and clinical tests are ordered that can hardly supply useful information. Our laboratory chiefs often complain of too many "slap-happy and shotgun" requests. Counting the cells in bloody and cloudy spinal fluid is like counting the hairs on a rabbit to see if it is a big rabbit or a little rabbit! In our hospital, blood is extracted routinely from the patient—before he even gets to bed—for the purpose of V.D.R.L. determination; although a positive turns up in less than 1:1000 cases. In 5 years, we have had 2 positive fluids, both of which were false positive.

There are times when we cannot avoid interfering with the blood chemistry, electrolyte balance or endocrine balance; and occasionally patients are out of balance when admitted. A remarkable amount of knowledge has accumulated on these subjects—but not enough! Speaking for myself, understanding these intricate reactions is difficult. I have more confidence in the body's automatic ability to control them—remembering what an incredible

* 899 Madison Avenue, Memphis 3, Tennessee.

variety of food, drink or other materials can be dumped into the stomach in almost any relative amounts and still perfect balance results. It may be safer as well as more comfortable to leave these matters to nature by simply avoiding anything that might upset the patient.

Nearly all neurosurgical procedures can be done satisfactorily and expeditiously with the patient lying on an ordinary operating table, but despite this, for almost every kind of operation, the patient is put in a different position. Ties are done with the patient sitting up jackknifed, with a complicated superstructure resembling an offshore oil rig. Operations on the cervical spine and cerebellum also are done with the patient sitting up, the surgeon working with his arms in the air, and the patient running the risks of hypotension and air embolism. Recently, seeing a neurosurgical friend struggling with a cerebellar tumor, with the patient insecurely anchored in this position, I could not resist asking if he had ever tried it standing up in a hammock! To remove a lumbar disc, some surgeons put the patient up on his elbows and knees—over a barrel, so to speak; and many even make a major procedure of ventriculography.

Next, the patient is draped in a manner as ritualistic and time-consuming as a Mormon wedding! Some surgeons spend a good deal of time sewing various layers to the scalp; only a few layers are necessary if one is an impervious plastic. Most neurosurgical operations may be carried out under local anesthesia, avoiding the hazards of both the anesthetic and the anesthetist; but multiple-drug anesthetics are employed, with amazingly complicated machines demanding nearly all of the anesthetist's attention. Endotracheal intubation is considered obligatory by many, but we find it seldom necessary. In the meantime, so-called heart block has increased from 1:5000 to 1:600, according to recent reports, requiring frantic thoracotomy and heart massage in order to save the patient's life, even if it is too late to save his brain. What a comfort to be free from the anxiety of having bleeding or other complications masked by residual anesthesia and to find the postoperative patient smoking, reading the papers or eating lunch after returning from the operating room! A study of mortality rates in 10 university hospitals revealed 1:4400 deaths attributed to nitrous oxide, 1:2000 to Pentothal or to spinal, and only 1:6000 when the operation was done under local anesthesia. The addition of curare more than doubled the mortality rate, with a peak of 1:62 when ether and curare were combined. To knock a patient unconscious and paralyze the respiratory centers in a minute and a half with a roughly estimated dose of Pentothal sodium (even when done by a medical anesthesiologist—as I have seen on occasions) is bound to be dangerous.

Blood is given almost routinely, being replaced rather than kept in the body. Some even take the blood out before operation and then return it. Patients who get only one pint of blood run all of the risks and probably do not need it in the first place—they can replace the blood loss the same way the donor does. Transfusions are now killing more patients than appendicitis. So persuasive are the transfusionists that we would believe them, if we had not done 5000 disc operations without giving any blood and with-

out losing a patient and 1000 craniotomies on tic patients with 1 transfusion for medical indication. Two of the tic patients died; one, the following day, the other, the following week. The employment of hypothermia and hypotension is still too recent to judge whether the risks are justified and should not lead to premature abandonment of tried methods.

The present-day postoperative patient is nauseated from anesthesia, his throat is sore from intubation, and he can neither rest nor sleep because of needles in his veins and a catheter in his bladder. He must put up with the sight of a bottle of blood hanging over his head, or a less appetizing one if his stomach is upset, with no effort even of concealment. To add to his troubles, a nurse pokes him in the rear end with a big and often blunt needle every few hours, administering antibiotics, although oral administration produces just as quick and just as high blood levels. I am sure that we have more surgical infections in this antibiotic era than in the days when we relied upon aseptic technique and physiologic handling of the tissues.

I am reminded of an instance where a surgeon who was a tedious operator and worked very hard on his patients after surgery, much concerned by their stormy and distressing postoperative course, asked the late Dr. Wilhelm Kohlmer how it was that his patients got along so smoothly and comfortably. Doctor Kohlmer's reply was, "As less you do, besser ist."

The practice of medicine by the simplest methods consistent with safety and effectiveness, I believe, is worth while in order to save time, effort, pain, blood and money. Surely, if the patient is not frightened, starved and dehydrated but allowed to eat, drink, smoke and generally follow his usual bent —including coffee and fruit juice in the morning before operation, if he is operated upon under local anesthesia, and if the natural openings are used for medication and fluid instead of the needle, his stay in the hospital is sure to be shorter and less exhausting physically and financially. Also, anticipating complications and preventing them, if possible, greatly simplifies the patient's course. The old rule that the physician should precede the disease, foreseeing and preventing complications rather than treating them, should be remembered.

Only the doctor is in a position to determine what measures are really indicated, and the public has a right to expect of him thoughtful discrimination.

HYPOTHERMIA IN THE SURGICAL TREATMENT OF RUPTURED INTRACRANIAL ANEURYSMS*

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HYPOTHERMIC anaesthesia for cerebrovascular surgery was begun in the Toronto General Hospital in the summer of 1954. This followed upon the general physiological studies of hypothermia by Bigelow and his co-workers,[1,2] the experimental studies of Lougheed and Kahn[7] regarding the effects of hypothermia in the prevention of cerebral anoxia, and the clinical experience of Lougheed *et al.*[8] using hypothermic anaesthesia for one case of arteriovenous malformation and one hemispherectomy for glioblastoma multiforme.

Cerebrovascular surgery presents all the difficulties encountered in the surgery of large vessels throughout the body and there are problems inherent in the relatively small size of cerebral vessels; even the internal carotid artery is small in proportion to the aorta, pulmonary artery or subclavian artery. The accurate repair of a ruptured aneurysm is facilitated by partial or complete interruption of the circulation, as described by Hamby,[5] so that surgery may be done in a dry field. The resultant cerebral ischemia may cause infarction of the brain. Hypothermic anaesthesia provides protection against anoxia and infarction, allowing occlusion of the blood flow for longer, though still short periods. Additionally, dissection of an aneurysm and manipulation of the cerebral artery bearing it may cause arterial spasm and traction damage to the perforating vessels with resulting anoxia. The deleterious effects of spasm may be avoided when hypothermia outlasts the spasm. The reduction in brain volume accompanying hypothermia provides a "slack" brain, facilitating exposure of an aneurysm of the circle of Willis.

The results of the treatment of ruptured aneurysms by intracranial repair two or more weeks following bleeding as reported by Norlén and Barnum,[10] Norlén and Olivecrona[11] and Falconer[4] show a low mortality and morbidity rate. The results of the direct surgical treatment of a large group of patients with ruptured aneurysms, approximating a consecutive series, within days following bleeding have not yet been reported. The value of early surgical treatment is difficult to assess for the natural history of a consecutive series of angiographically verified aneurysms is not yet available as a control.

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McKissock and Walsh[9] have most nearly achieved a control series and have made a strong case in support of very early surgical treatment. Logue[6] has reported encouraging results in the early treatment of anterior cerebral aneurysms by clipping the anterior cerebral artery.

It is the primary purpose of this paper to report our experience with hypothermic anaesthesia in the management of ruptured aneurysms at varying stages and particularly in the first week following haemorrhage.

TECHNIQUE OF HYPOTHERMIC ANAESTHESIA

Between the summer of 1954 and January 1, 1957, no major change was made in the method of surface cooling described by our group in 1956.[3] Preoperative medication consisted of Laborit's lytic cocktail, chlorpromazine, promethazine, and Demerol, 50 mg. of each. This was administered the night before operation and was repeated approximately 2 hours before operation. At the time anaesthesia was induced, a slow intravenous drip of normal saline containing 50 mg. each of these three drugs in 250 cc. was started. Anaesthesia consisted of nitrous oxide and trichlorethylene administered by a continuous high-flow, non-rebreathing, non-carbon dioxide absorption technique. Surface cooling in a bath using crushed ice and water followed, and re-warming by means of warm water was commenced as soon as the intracranial operation was completed.

Various rates of re-warming have been carried out. Certain modifications evolved in this technique and practised during the later cases may be summarized here. With a view to avoiding systemic hypotension and the administration of norepinephrine (Levophed) the dosage of chlorpromazine has been reduced and promethazine has been eliminated as a pre-operative sedative. Re-warming has been achieved by filling the tank with water at approximately 38.0°C. and as soon as the patient's temperature is above 30°C. and is rising, the patient is removed from the bath, carefully dried, placed in a bed and covered with flannelette sheets and surrounded with water bottles at a temperature of 37°C. The patient is kept in a recovery room immediately adjoining the operating room and oxygen is administered by nasal catheter. The foot of the bed is elevated, and careful watch is kept on the blood pressure.

Shivering has been minimized by increasing the depth of anaesthesia and small doses (25 mg.) of chlorpromazine are used during the operation and postoperatively as required.

In elderly patients, or patients with evidence of atherosclerosis, arteriosclerosis and hypertension, our aim has been to avoid lowering the temperature below 30°C. In younger patients with no apparent cardiovascular disorder, the minimum temperature has commonly ranged between 28.6°C. and 30°C.

RESULTS AND COMPLICATIONS ATTRIBUTED TO HYPOTHERMIA

Hypothermic anaesthesia has been utilized in 88 cases of cerebral vascular problems consisting of 73 cases following rupture of a berry aneurysm,

1 case of an unruptured berry aneurysm, 8 cases of internal carotid artery thrombosis or stenosis in the neck, and 6 of arteriovenous malformation. One death resulted from irreversible ventricular fibrillation. A second case of ventricular fibrillation occurred which was reversible and is the only other example of cardiac arrest in the group of cerebrovascular problems.

Among 68 cases closely studied visually by the Smith-Stone cardiograph, by continuous ink-written electrocardiographic record and spot regular electrocardiographic tracings, the following dysrhythmias were identified: wandering pacemaker 12, auricular fibrillation 1, auricular flutter and frequent ventricular extrasystoles 1. Sinus arrhythmia was relatively common. Cardiac dysrhythmia has been less common among later cases. We have attributed this improvement, as suggested by Pool,[12] to the maintenance of deeper anaesthesia, and to the elimination of respiratory depression by anaesthesia.

Hypothermia and Surgery. The evaluation of hypothermic anaesthesia in our cases of ruptured aneurysms cannot be divorced from the surgical problems involved in defining and occluding the common carotid and vertebral arteries in the neck and in operating upon the recently ruptured aneurysm. It will be necessary therefore to consider later the interrelated problems of surgical treatment and hypothermic anaesthesia.

SURGICAL MANAGEMENT

Intracranial clipping or ligation of the aneurysm is preceded by isolation of the common carotid and vertebral arteries in the neck. For the acute cases, a generous exposure is used, and a large subtemporal decompression is provided in each instance. Originally, the cervical vessels were occluded only if haemorrhage developed. More recently, the common carotid arteries have been occluded immediately before application of clip or ligature to the aneurysm. This has diminished the tension in the aneurysmal sac, preventing the clip or ligature tearing the taut sac.

POLICY AND SELECTION OF CASES

Our policy has been to perform bilateral carotid angiography the day of admission to hospital in each case of subarachnoid haemorrhage, and to operate upon a ruptured aneurysm the following day. In the event that a massive clot is causing deepening coma, immediate operation has been performed. This policy was followed, save that decerebrate rigidity and akinetic mutism were considered contraindications to operation after the first 23 cases. Additionally, following consultation, certain patients have not been transferred from other hospitals to the neurosurgical service and our unit for widely varying reasons including advanced age, unwillingness to accept operation and multiple aneurysms. This has not been a large group, and we estimate it to consist of about 10 cases. One patient admitted to the neurosurgical service died without operation.

Additional factors bear on the composition of this series of patients. They were received directly from house, hotel or place of work; they were trans-

ferred from other hospitals at a distance, after intervals varying from hours to weeks following the initial haemorrhage, or following a recurrent haemorrhage, often in a critical condition.

The site and size of the aneurysm, recurrent haemorrhage, massive intracerebral clot, ischemic softening of brain, obstructive or communicating hydrocephalus, the interval between haemorrhage and operation, and the persistence of arterial spasm, are all factors bearing upon the outcome of operative therapy. The age of the patient, atherosclerosis, hypertension and arteriosclerosis, and such diseases as diabetes in turn bear upon the individual's capacity to withstand the effects of haemorrhage and intracranial operation.

In an attempt to sum up these variable factors as they bear upon the individual case, Botterell *et al.*[3] graded cases as to operative risk from 1 to 5. "Grade 5 represents a moribund or nearly moribund patient with failing vital centres and extensor rigidity. Grade 4 includes patients with major neurological deficit and deteriorating because of large intracerebral clots or older patients with less severe neurological deficit but pre-existing degenerative cerebrovascular disease. Grade 3 represents the drowsy patient with a neurological deficit and probably an intracerebral clot. Grade 2 indicates a drowsy patient without significant neurological deficit. Grade 1 indicates a patient who is conscious with or without signs of blood in the subarachnoid space." Since these grades were established, it has become clear that insufficient emphasis was laid upon ischemic infarction of the brain caused by thrombosis or spasm of the artery bearing the aneurysm, upon the existence of communicating hydrocephalus, and upon age accompanied by degenerative vascular changes.

These authors also classified the results of surgical treatment in the surviving patients. "*Excellent result*" means that the patient is well and has no neurological deficit. "*Good result*" indicates that there is a persistent neurological deficit that is not disabling. "*Fair result*" indicates normal mentality and speech, but disabling neurological deficit. "*Bad result*" indicates mentally retarded and dysphasic patients and those with a major neurological deficit, e.g. hemiplegia or blindness would be classified as bad.

No patient has been operated upon intracranially when a large aneurysm existed (usually in the region of the bifurcation of the internal carotid artery) and the origin of the aneurysm could not be established.

RESULTS

INTERNAL CAROTID ARTERY

The results following intracranial surgical treatment of ruptured aneurysms of the internal carotid artery are summarized in Table 1.

In 16 cases (14 supraclinoid and 2 bifurcation) operation was performed after 1 week had elapsed from the last intracranial haemorrhage, without mortality. Five deaths occurred among the 14 patients operated upon within 1 week of the last haemorrhage. Surgical treatment during the first week involved operating upon 4 patients during the first 24 hours and 4 additional

TABLE 1

Internal carotid—30 cases

Pre-operative Risk	0–7 Days		8–14 Days		Over 2 Weeks	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
1	7	0	3	0	11	0
2	2	0				
3*	2	2			2	0
4	2	2				
5†	1	1				
Total	14	5	3	0	13	0

* Two deaths, risk 3, represent preventable technical errors.
† One death, risk 5, represents "salvage" surgery following recurrent haemorrhage.

patients during the second 24 hours following bleeding. Of 14 patients operated upon during the first week, 7 had had recurrent haemorrhage. All the 25 survivors, whether operated upon early or late, were graded as "excellent" or "good" (Table 2).

TABLE 2

Internal carotid

25 survivors—3 years to 5 months following operation

Risk	0–7 Days	8–14 Days	Over 2 Weeks
1	5 Ex. 2 Good	2 Ex. 1 Good	8 Ex. 2 Good
2	1 Ex. 1 Good		
3			2 Ex. 1 Good

Deaths: Case Summaries

Case 73, risk 3, age 56. Interval 36 hrs., single haemorrhage. Operative haemorrhage was the problem in this case, involving many periods of occlusion of the cervical arteries and transient clipping intracranially of the internal carotid artery. Marked spasm developed as manipulation of the internal carotid continued. This was followed by the development some hours postoperatively of hemiplegia caused by ischemic softening of the frontal and temporal lobes and death. Death resulted from technical operative errors.

Case 37, risk 3, age 32. Interval 48 hrs., single haemorrhage. A subdural clot was found at operation but an intraventricular clot was not suspected. At autopsy, a large intraventricular clot was found and was attributed to postoperative bleeding.

Case 30, risk 4, age 43. Interval 12 hrs. after initial bleeding. This patient was a diabetic and a known hypertensive. There was extensive softening of the left frontal lobe with a large intracerebral clot, the whole damaged area extending 12 cm. from the left frontal pole. Brain damage was judged to be overwhelming and further

aggravated by clipping the internal carotid artery as well as the aneurysm. Hypotension accompanied anaesthesia.

Case 36, risk 4, age 55. Interval 4 days, recurrent haemorrhage. She was a known hypertensive. On the *second* postoperative day ischemic softening of the temporal lobe developed. She became vegetative and finally died in a hospital for the chronically ill. Pre-operative blood pressure was 180/90. It fell to 75 for a period of 10 min. during operation and ranged from 75 to 90 systolic for 40 min. She required norepinephrine (Levophed). The common carotid and vertebral arteries were not occluded.

Case 10, risk 5, age 41.* Interval 4 hrs., recurrent haemorrhage; decerebrate rigidity and fixed and dilated pupils had developed pre-operatively because of coning secondary to a large clot in the temporal lobe. He was, in fact, moribund before he was operated upon.

ANTERIOR CEREBRAL-ANTERIOR COMMUNICATING ARTERY

There was 1 death among 9 patients operated on 1 week or more after rupture. Of 20 patients operated on within 7 days following the last haemorrhage, 9 died (Table 3). Five patients were operated upon within the first 24 hours, and 5 during the second 24 hours. There were 9 recurrent haemorrhages among those 20 cases. Table 3 shows the results.

TABLE 3

Anterior cerebral-anterior communicating

Pre-operative Risk	0–7 Days		8–14 Days		Over 2 Weeks	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
1	6	2	1	0	5	0
2	5	2			2	0
3	2	0				
4*	7	5	1	1		
5						
Total	20	9	2	1	7	0

* 4 deaths, risk 4, represent "salvage" surgery in cases of recurrent haemorrhage.

Deaths: Case Summaries

Case 35, risk 1, age 41. Single haemorrhage, interval 44 hrs. This man, with chronic Bright's disease, made an uneventful postoperative recovery until the 3rd day when a complete hemiplegia developed insidiously because of thrombosis of the anterior cerebral and middle cerebral and internal carotid arteries. His postoperative course was complicated by hypotension and he required norepinephrine (Levophed) for a period of 36 hrs. He was extremely sensitive to this drug and there were numerous, short, sharp drops of blood pressure to the neighbourhood of 80. His pre-operative blood pressure was 160/85. During operation this patient's right

* This case was described in detail in a previous report.[3]

common carotid artery was occluded for 7½ min. at 29°C. and on two additional occasions both common carotid arteries were occluded for 3 min. and 4 min. respectively. The systemic blood pressure never dropped below 120.

Case 45, risk 1, age 21. Interval 48 hrs., single haemorrhages. Because of rupture of the aneurysm before it was exposed and subsequent technical difficulties, the patient was hemiplegic and mute following operation. The mean blood pressure was 52 for 10 min. during the period of haemorrhage. Both common carotid arteries were shut off on one occasion for 5½ min. at a temperature of 30.2°C. together with both vertebral arteries for 4½ min. The right frontal lobe was resected at operation and showed no significant abnormality of the arteries on microscopic examination.

At autopsy 1 month following operation there was a most unusual degeneration of intima, media, and adventitia of the arterial walls, the significance of which is unknown. This patient's death was attributed to very early rupture of the aneurysm and excessive retraction on frontal lobe, hypothalamus and region of the 3rd ventricle.

Case 68, risk 2, age 42. Interval 48 hrs., initial haemorrhage. Hemiplegia developed 3 days following operation at which the aneurysm and the left anterior cerebral artery were clipped. It was uncertain whether thrombosis had developed or a postoperative clot became manifest. The wound was opened and a very small amount of clot was present. The bone flap was removed. A postoperative infection of the wound then developed, and he died 6 weeks following the second operation from recurrent haemorrhage.

A loosened clip was found at postmortem examination. It was uncertain whether this was the cause of the fatal haemorrhage or whether it was a secondary septic haemorrhage. There was no significant change in blood pressure throughout hypothermic anaesthesia and re-warming.

Case 58, risk 2, age 52. Interval 4 days, initial haemorrhage. Recovery following operation was uneventful for 12 hrs. when coma developed because of a postoperative clot. Seven days later she became hemiplegic and comatose. She never recovered consciousness, and died some 8 weeks later in a hospital for the chronically ill. No postmortem examination was obtained.

Case 38, risk 4, age 56. Interval 24 hrs., recurrent haemorrhage. This patient was semicomatose, with a right hemiplegia, papilloedema, and deepening coma. There was an azygos anterior cerebral artery with the aneurysm projecting backwards from the anterior cerebral-anterior communicating junction. Clipping of the aneurysm was inadequate and was reinforced with muscle. Gradually, over a period of days, recovery occurred when he again commenced to deteriorate. Ventriculography showed a haematoma in the septum lucidum and large lateral ventricles. The clot was evacuated. Autopsy showed clot in the septum lucidum, the left frontal lobe and the region of the anterior communicating artery, and hydrocephalus.

Hypothermic anaesthesia and cardiovascular function throughout the operation and postoperative course were not unusual. The common carotid and vertebral arteries were occluded bilaterally for 5¼ min. at 29.6°C. with a systolic blood pressure of 90/60 on one occasion, and on a second occasion the common carotid arteries were occluded bilaterally for 3¼ min. at 30.4°C. The right common carotid artery was occluded for 1 min. and the left common carotid for 5 min. at 30°C.

Comment. This patient's technical problems with reference to the aneurysm were not adequately handled at operation. With the development of appropriately curved, clip-bearing forceps, this should not be the case in future.

Case 44, risk 4, age 47. Interval 24 hrs., recurrent haemorrhages (3 within 3 weeks). Following an angiogram prior to admission serial seizures and hemiplegia had developed. Blood pressure was 210/120. At operation the aneurysm was clipped. Difficulty because of haemorrhage required 5 periods of occlusion of cervical vessels, as follows: both carotids for 6 min. with the vertebrals for 3½ min.; then bilateral carotids for 4, 4, 3 and 2¼ min., the temperature ranging from 30.8°C. to 30.6°C. The patient had a subdural clot which was evacuated. Her blood pressure fell from 142/70 to 62/45 for 15 min. and then was maintained at 80 to 100 with norepinephrine (Levophed) for 6½ hrs. A second drop in blood pressure to 70 mm. accompanied re-warming, requiring additional norepinephrine (Levophed). The patient remained hemiplegic and vegetative, finally dying in a hospital for the chronically ill. Autopsy was not obtained.

Case 20, risk 4, age 50.* Interval 48 hrs., single subarachnoid haemorrhage. The patient was a known hypertensive. She became hemiplegic following angiography. The aneurysm was clipped. The cervical vessels were not occluded. Blood pressure prior to operation ranged from 190/110 to 220/100. It fell to 150 systolic following the administration of chlorpromazine and later dropped to 125 systolic for 5 min. On the 3rd postoperative day, the patient became comatose, and at autopsy some 2 months later both anterior cerebral arteries were thrombosed. The silver clips had not encroached upon the anterior cerebral arteries. Twenty-four hours following the initial operation, the right frontal lobe was resected because of cerebral swelling. Her low temperature was 30.8°C.

Case 27, risk 4, age 22. Interval 4 days, recurrent haemorrhage. This patient had multiple congenital malformations, including coarctation of the aorta with paraplegia. The left arm was paralyzed also. Operation demonstrated a subdural haematoma, which was evacuated. The aneurysm was clipped. Bleeding required that both common carotid and vertebral arteries should be occluded for 5 min. at 29.4°C. A period of apnoea accompanied the occlusion of the vertebral arteries. The paraplegia persisted. Convulsions, which had occurred pre-operatively, recurred postoperatively. He was demented and was finally transferred to a mental hospital where he died. Hypothermic anaesthesia was uneventful.

Case 70, risk 4, age 65. Interval 6 days, single haemorrhage. He was drowsy and disorientated prior to operation. His history suggested that he had suffered an old thrombosis of the posterior inferior cerebellar artery. Both anterior cerebral arteries were in intense spasm at the end of the operation. Hypothermic anaesthesia was accompanied by a drop in blood pressure from a pre-operative level of 140/80 to 60/40 for 10 min. and 75/45 for an additional 60 min. The common carotid and vertebral arteries were occluded bilaterally for 1 to 2 min. prior to clipping the aneurysm. Postoperatively, he never recovered consciousness. There was extensor rigidity of the arms and legs. An autopsy could not be obtained.

* This case was described in detail in a previous report.[3]

Comment. It seemed probable that basilar artery thrombosis or occlusion by an embolus had occurred. It appears that systemic hypotension and occlusion of the vertebrals and perhaps also the common carotid arteries contributed to embolism or thrombosis of the basilar artery.

Case 69, risk 4, age 65. This man was a known, mild hypertensive, and had an interval of 10 days between his last subarachnoid haemorrhage and operation. He had had three haemorrhages, one in June, one on September 10, and the third on September 11, 1956. Ten days pre-operatively, the third subarachnoid haemorrhage developed with severe headache, nausea and drowsiness. The following day, he became confused and disorientated and had a staggering gait. Over the next 10 days there was steady deterioration in the level of his consciousness with a drift of the right arm, and marked stiffness of the neck. There were bilateral upgoing toes, and the blood pressure was 190/110. On October 11, under hypothermia, the aneurysm was clipped uneventfully, and a resection of the right frontal lobe was carried out.

Postoperatively the patient was placed on Dicumarol to prevent thrombosis. One month after operation, the left anterior communicating artery failed to fill. There were no localized neurological signs, and the patient was discharged to a hospital for the chronically ill. At the time of discharge, he was relatively unchanged from the pre-operative state. Pneumoencephalogram prior to discharge showed a communicating hydrocephalus.

Surgical therapy in Cases 38, 44, and 27 which we judged to constitute "salvage" surgery has proved unsuccessful. In one instance, Case 38, it would appear that had the aneurysm been successfully handled at the initial operation, recovery might have been achieved.

Survivors. The survivors, 19 in all, include 16 "excellent" or "good" results, and 3 "bad." One of the 3 "bad" survivors was a grade 4 operative risk (Table 4).

MIDDLE CEREBRAL ARTERY

Of this group of 14 patients, 10 were operated upon within 7 days with 2 deaths, and there were no deaths among the 4 patients operated upon after 1 week or more had elapsed from the last bleeding (Table 5).

Among the 10 patients operated upon within 7 days of the last haemor-

TABLE 4

Anterior cerebral-anterior communicating

19 survivors—3 years to 5 months following operation

Pre-operative Risk	0–7 Days	8–14 Days	Over 2 Weeks
1	4 Ex.	1 Ex.	4 Ex. 1 Bad
2	2 Ex. 1 Good		1 Ex. 1 Bad
3	1 Ex. 1 Good		
4	1 Good 1 Bad		
5			

TABLE 5

Middle cerebral

Pre-operative Risk	0–7 Days		8–14 Days		Over 2 Weeks	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
1				0	3	0
2	1	0				
3*	3	1				
4†	6	1	1	0		
5						
Total	10	2	1	0	3	0

* 1 death, risk 3, followed upon acute gastric dilatation, pneumonitis and anuria.

† 1 death, risk 4, in hypertensive diabetic patient, caused by ischemic softening judged to antedate operation.

rhage, 4 had suffered recurrent bleeding. Three of the 10 patients were operated upon within the first 24 hours. During the second 24 hours an additional 3 were operated upon. Six of the 10 patients operated on during the first week had a large clot in the temporal lobe.

Deaths: Case Summaries

Case 57, risk 3, age 50. Interval 12 hrs., recurrent haemorrhage. Deteriorating consciousness with a left hemiplegia resulted from a large clot in the temporal lobe. Following removal of the clot, the aneurysm was clipped. During operation, acute gastric dilatation developed and the patient inhaled some of his vomitus. He was a known hypertensive with a pre-operative blood pressure of 180/90. This fell to 70/55 for 25 min., thereafter running from 110/65 to 80/60 for 4½ hrs. No occlusion of the cervical arteries was carried out. His low temperature was 31.0°C. Postoperatively, his neurological deficit was recovering satisfactorily and he was improving in his level of consciousness. There developed oliguria going on to anuria, and pneumonia and he died.

Case 21, risk 4, age 50.* Interval 5 days, recurrent haemorrhage. She was semicomatose, hemiparetic, a diabetic, and a known hypertensive, with blood pressure of 220/100. At operation, the aneurysm on the right middle cerebral artery was clipped. She never recovered consciousness and died approximately 2 days following operation. There were no cervical arterial occlusions. Her blood pressure during cooling and operation dropped to 90/70 for 5 min. and the systolic pressure remained from 100 to 140 for a period of 2 hrs.

Autopsy revealed softening in the distribution of the middle cerebral artery which was judged to antedate operation. There was substantial cerebral swelling and it appeared that the subtemporal decompression which had been created was inadequate. This is another example of the tendency to ischemic softening in hypertensive or arteriosclerotic and atherosclerotic patients with a ruptured aneurysm. No thrombus or embolus was demonstrated in the middle cerebral artery at postmortem examination.

* This case was described in detail in a previous report.[3]

TABLE 6

Middle cerebral

12 survivors—3 years to 5 months following operation

Pre-operative Risk	0–7 Days	8–14 Days	Over 2 Weeks
1			2 Ex. 1 Good
2	1 Ex.		
3	1 Ex. 1 Good		
4	2 Ex. 1 Good 2 Bad	1 Bad	
5			

The 12 survivors are of unusual interest for they include 6 excellent and 3 good results; 3 were bad (Table 6).

This striking degree of recovery developed although the feature of this group of ruptured aneurysms of the middle cerebral artery is the high incidence of massive clots in the temporal lobe causing hemiplegia and deepening coma. This high incidence of large clots contrasts with the relatively low incidence of significantly large clots secondary to rupture of anterior cerebral aneurysms, in this series. The paucity of middle cerebral aneurysms presenting for surgical treatment later than 2 weeks following haemorrhage is striking when compared with aneurysms of the internal carotid artery and in less degree with aneurysms of the anterior cerebral-anterior communicating complex.

DISCUSSION

Included in each group of aneurysms are cases of initial and recurrent haemorrhage accompanied by varying degrees of pre-operative cerebral damage from ischemic softening and hydrocephalus occurring in patients of widely varying age and suffering various degrees of general vascular pathological changes. These variables and the relatively small number of cases make it difficult to draw far-reaching conclusions. Table 7 illustrates the dif-

TABLE 7

Total mortality 23.2 per cent

73 cases—17 deaths

Location	0–7 Days		8–14 Days		Over 2 Weeks	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
Internal carotid	14	5	3	0	13	0
Anterior cerebral-anterior communicating	20	9	2	1	7	0
Middle cerebral	10	2	1	0	3	0
Total	44	16*	6	1	23	0

* 4 of these deaths occurred late in hospitals for chronically ill.

ference following operation upon patients who have survived for 7 days and those treated during the first week, using the same surgical and hypothermic anaesthetic technique.

The first week, particularly the first 24 hours, is a period of high mortality, as shown by Walton[13] and others, with medical management. Successful operation is necessary during this time to treat the effects of the initial haemorrhage such as a clot and to prevent the recurrent haemorrhages common during the second week. Selection of cases for operation, we believe, can be achieved only by clinical assessment and early angiography identifying the site and size of the aneurysm and indicating the presence or absence of a large clot. This conviction exists though in 3 cases serious, and in 3 cases minor reactions occurred during angiography. We are now using Thorotrast in selected cases.

The result that may be anticipated from early operation is governed by a number of factors:

(a) *Site of Aneurysm.* Rupture of an aneurysm of the *middle cerebral* artery at the bifurcation or trifurcation of the artery produces in a high percentage of cases an intracerebral clot of lethal size. Operation and evacuation of the clot within 24–48 hours may be essential to survival. The merit of the clinical result will depend on the extent of brain injury and whether or not the dominant hemisphere is badly damaged.

A patient with bleeding from an aneurysm of the *anterior cerebral-anterior communicating* complex accompanied by coma or semicoma with hemiparesis or hemiplegia and without a significantly large clot has proved a *bad risk* for early (within 7 days) operation. We have not seen any such case late. It appears that spasm has resulted in ischemic damage in the region of the third ventricle and adjacent deep structures. The proximity of aneurysms of the anterior cerebral artery to the septal area and region of the third ventricle makes operative manipulation hazardous.

Ruptured aneurysms of the *internal carotid* artery, unless large, should be readily accessible whether at the bifurcation or at the level of the posterior communicating artery. Arterial spasm has not commonly caused ischemic softening, we believe, either before or as a result of operation. Our results in grades 3, 4 and 5 have been bad, but we believe that they can be improved by further advances in operative technique.

(b) *Ischemic Infarction of Brain.* Ischemic infarction is recognized as a complication following rupture of an aneurysm, without operation. Following operation under 7 days thrombosis has been a greater problem with aneurysms of the anterior cerebral-anterior communicating complex, a group of small arteries, than with operations for aneurysms of the internal carotid. Regardless of the site of the aneurysm, atherosclerotic, arteriosclerotic hypertensive patients are vulnerable to this complication following operation. Thrombosis has not been a problem following operation when a week or more has elapsed since the last haemorrhage, save in one case. This emphasizes, we think, the importance of arterial spasm in the acute phase.

Factors contributing to aggravation of arterial spasm in turn leading to

ischemic softening or thrombosis and infarction may be divided into two major groups: (1) Local factors enhancing arterial spasm. (2) Systemic factors reducing cerebral blood flow for significantly long periods of time.

1. *Local factors enhancing arterial spasm and its effects.* Trauma to the wall of the vessel, such as excessive traction or pinching with an over closely applied clip, may increase arterial spasm. The presence of an atheromatous plaque in the arterial segment suffering spasm enhances the resulting ischemia.

2. *Systemic factors reducing cerebral blood flow* for significantly long periods enhance the effects of arterial spasm. Thus situations contributing to thrombosis or ischemic infarction may be listed as follows:

(i) Haemorrhage of sufficient degree to lower the blood pressure and impair cerebral circulation for an excessive period.
(ii) Reduction of blood pressure caused by chemical agents used in producing anaesthesia, such as chlorpromazine.
(iii) Operating upon the patient with the head unduly elevated.
(iv) Possibly occlusion of the common carotid and vertebral arteries in the face of a stenosed atheromatous cerebral artery in spasm.
(v) The question arises of "rebound" increased coagulability of the blood following hypothermia.

Reduction of the effects of these factors contributing to ischemic infarction, or thrombosis, is of importance.

Cerebral swelling is a common sequel to subarachnoid and intracerebral haemorrhage in the days following the ictus. Operation, exposure and retraction of the brain and further interference with cerebral circulation by clipping and coagulating cerebral veins aggravate cerebral swelling, particularly in the case of aneurysms of the anterior cerebral artery. The problem exists as to whether or not cerebral swelling can be related to the development postoperatively of thrombosis or ischemic softening.

TABLE 8

Age: Mortality

73 cases

Location and Age	0–7 Days		8–14 Days		Over 14 Days	
	No.	Died	No.	Died	No.	Died
Internal carotid						
Below 50	9	3	2	0	11	0
50 and over	5	2	1	0	2	0
Anterior cerebral-anterior communicating						
Below 50	14	5	1	0	5	0
50 and over	6	4	1	1	2	0
Middle cerebral						
Below 50	6	0	1	0	3	0
50 and over	4	2	0	0	0	0
Total						
Below 50	29	8	4	0	19	0
50 and over	15	8	2	1	4	0

(c) *Age and Mortality.* Table 8 indicates the influence of age upon the outcome of the direct intracranial attack upon aneurysms during the first week following an initial or recurrent haemorrhage. Of the 29 patients under the age of 50, 8 died. Of the 15 patients over 50, 8 died.

HYPOTHERMIC ANAESTHESIA

Hypothermia has provided protection against anoxia during occlusion of common carotid and vertebral arteries and has reduced brain volume. There has been no instance of anoxic encephalopathy attributed to cervical arterial occlusion. Bilateral cortical blindness occurred in one case and is believed to have resulted from an embolus arising as a result of the formation of a mural thrombus at the site of compression of the vertebral artery.

Reduction in brain volume from hypothermia has proved of assistance to the surgeon, particularly in the acute case.

SUMMARY

1. Following haemorrhage, 73 patients with ruptured berry aneurysms have had the aneurysm operated on using hypothermia, and common carotid and vertebral arteries were occluded as necessary.

2. There were 17 deaths, and of the 56 survivors, 50 were excellent or good results and 6 were bad or fair. One death occurred when 1 week had elapsed between haemorrhage and operation. Forty-four patients were operated on under 7 days with 16 deaths.

3. The results of operation in the first 7 days following haemorrhage vary according to (a) the site of the aneurysm, (b) the extent of brain injury from haemorrhage or ischemic softening, (c) the presence or absence of a large haematoma, and (d) the physiological age of the patient.

CONCLUSIONS

1. We believe that hypothermia and cervical arterial occlusion as required have improved our surgical treatment of ruptured aneurysms.

2. Carotid angiography should be performed as early following a subarachnoid haemorrhage as is judged practicable, followed by decision regarding operation.

3. Our experience indicates that early operation is of great value in cases of middle cerebral aneurysms with large intracranial clots. Patients with anterior cerebral aneurysms with coma or semicoma and hemiplegia without a haematoma have not done well following direct attack upon the aneurysm within 7 days of rupture, particularly elderly arteriosclerotic patients (Grades 3–5). We do not judge our results in cases of internal carotid aneurysms—patients graded 3–5 operated on during the first week represent what should have been achieved in these cases because of preventable technical errors in 2 cases, and one operation on a moribund patient.

4. Improvement in the outlook of patients with a ruptured aneurysm requires further research, refinement of angiography, anaesthesia and surgery. Arterial spasm is a major problem in the acute cases.

5. Surgical treatment, if it is to reduce the mortality, must follow early upon haemorrhage before the development of irreversible brain injury.

TABLE 9

Subsequent cases

Location	Interval 0–7 Days		Interval Over 7 Days	
	Cases	Deaths	Cases	Deaths
Internal carotid	12	2	4	0
Middle cerebral	3	0	0	0
Anterior cerebral	5	1	0	0
Total	20	3	4	0

ADDENDUM

Since the series of cases reported in this paper was completed, 24 additional patients with ruptured aneurysms have been operated on using the same technique (Table 9).

The authors wish to acknowledge their appreciation of the cooperation and collaboration they have received from the neurological staff of the Toronto General Hospital (Doctors Hyland, Richardson, Walters and Barnett) and to our medical colleagues who have initiated the treatment of these patients.

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RETINAL ARTERY BLOOD PRESSURE MEASUREMENTS IN DIAGNOSIS AND SURGERY OF SPONTANEOUS CAROTID OCCLUSIONS

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RECENT interest in vascular surgery of atherosclerosis has been extended to the carotid system. Undoubtedly, the possibility of surgical relief of spontaneous carotid occlusions will be explored further despite the relatively few encouraging reports as yet available.[5,6,9,10,19] The comparatively bad prognosis of the untreated lesion makes early diagnosis of the occlusions mandatory if therapy, either medical or surgical, is to be effective before important nervous function is lost. Comparative studies of retinal artery pressure can materially and safely aid the physician in diagnosis of these vascular occlusions if carefully integrated in diagnostic judgment.

While the determination of retinal artery blood pressure or ophthalmodynamometry is subject to limitations so far as absolute values are concerned, there is good evidence for its validity in comparing pressures in the two eyes. From differences in such readings one is entitled to make inferences in regard to comparative pressures in the parent internal carotid arteries.

In a normal carotid system pressure in the major intracranial branches (taken by direct measurement) is almost equal to that in the cervical internal carotid.[2] The pressure gradient downward from large to small vessels is uniformly progressive but the over-all drop is not great. Bakay and Sweet[2] have found after clamping the common carotid that the absolute drop in pressure throughout the carotid system on the same side is marked but the gradient of drop remains about the same as that before occlusion. It seems reasonable to assume that pressure in the ophthalmic and retinal arteries will parallel that in comparable branches of the carotid tree and will approximate the pressure in the internal carotid artery on the same side. Rand[16] has in one case compared the retinal artery pressure readings with directly measured pressure in the internal carotid artery and found a rather close correlation.

OPHTHALMODYNAMOMETRY

The technique of ophthalmodynamometry generally used is that of Bailliart.[1] It was described by Magitot[14] in 1922 and elaborated by Weigelin and Müller.[24] This relatively simple clinical procedure has been illustrated and described in detail by Thomas and Petrohelos,[21] Svien and Hollenhorst,[20] and by Heyman *et al.*[12] The ophthalmodynamometer is a small cylinder with

spring-loaded plunger and attached rod with footplate for application of pressure to the optic globe. The plunger is calibrated in grams.

After anesthetizing the conjunctivae and dilating the pupils, the footplate is placed against the eyeball at the outer canthus and pressure is applied progressively while the operator observes the major branches of the retinal artery. The diastolic pressure reading is that which is associated with the first visible distinct pulsation of the vessels, while the systolic pressure is that which is associated with collapse of the vessels. The readings in grams can be converted to millimeters of mercury by use of a conversion table which takes into account the already existing intraocular pressure. Since the direct readings in grams under conditions of normal intraocular pressure correspond closely to those for millimeters of mercury in the conversion table and since we are concerned primarily with comparative measurements in the two eyes, we have recorded only the figures taken directly from the instrument scale.

Retinal artery pressures have been measured in healthy adults and in patients with neurological diseases not associated with apparent vascular insufficiencies. Thomas and Petrohelos[21] reported that in their subjects the difference in *diastolic* pressures in the two eyes ranged from 0 to 15 per cent of the highest figure while the difference in *systolic* pressures ranged from 0 to 12.2 per cent. The average of the percentage differences in a larger number of subjects was 5.2 for diastolic and 3.3 for systolic pressures.

OPHTHALMODYNAMOMETRY AS AN AID IN THE DIAGNOSIS OF SPONTANEOUS OCCLUSION OF THE CAROTID ARTERIES

In analyzing the ischemic brain syndrome in 107 proved cases of spontaneous carotid occlusion, Johnson and Walker[13] found that the locus of obstruction was at the origin of the internal carotid artery in 81 of 97 cases in which this artery alone was involved. Many of these patients were suspected of harboring an intracranial tumor. It is evident that some method of clinical examination that might provide diagnostic information relating to occlusion of the internal carotid artery, in lieu of or at least before angiography, would be quite welcome. Ophthalmodynamometry does appear to be valuable in this regard.*

Thomas and Petrohelos[21] reviewed 19 cases of carotid occlusion from various causes. Only 4 failed to show a significantly lower pressure in the retinal artery on the side of the occlusion. The average percentage difference between the two sides for diastolic pressure was 31.7 and for systolic pressure was 24.1. Svien and Hollenhorst[20] recently reported 4 cases of unilateral thrombosis of the internal carotid in which they found the difference in diastolic retinal artery pressures on the two sides to range from 25 to 59

* We[22] have repeated previously performed studies of the effect of digital compression of the common carotid artery on ipsilateral retinal artery pressures and have found that this maneuver causes an average acute drop of 50 per cent in both systolic and diastolic readings. There was considerable variation among the several subjects. Ophthalmodynamometry is of value in the management of patients undergoing therapeutic carotid ligations.

per cent. They consider a comparison of diastolic pressures more reliable than that of systolic pressure on the two sides. They noted, however, that if the diastolic pressure in both eyes is less than 20 grams, any difference in the pressure readings on the two sides is not to be considered reliable for interpretation.

Heyman *et al*[12] in 16 cases of partial or complete occlusion of an internal carotid artery (verified by angiography in 14 of the cases) found the mean decrease in retinal artery pressure to be 27 per cent for the diastolic and 30 per cent for the systolic pressure on the side of the occlusion. They believe that a reduction of 25 to 30 per cent in both systolic and diastolic retinal artery pressures is diagnostic of impaired carotid circulation on the side of the lower reading. They pointed out that any conclusion to be drawn from the comparative studies of pressures in the two eyes is based on the assumption that the carotid circulation on one side is relatively normal. They believe, as we do, that both systolic and diastolic readings are important. Some of their patients with impaired carotid circulation showed a decrease in systolic readings only.

Weigelin and co-workers[23] found that the diagnosis of internal carotid thrombosis could be made by the aid of dynamometry in 6 cases, 2 of which were verified by operation. In 1 case angiography did not show filling on one side and there was no corresponding pressure difference.

When it is realized that thrombosis of the cervical internal carotid is in some instances amenable to surgery and that in such cases early diagnosis and prompt efforts at alleviation of the obstruction are important, then the information provided by a comparative measurement of retinal arterial pressures on the two sides becomes of considerable significance. We are submitting our findings in 3 cases of internal carotid thrombosis. The diagnosis was confirmed by direct exploration in 2 cases and by angiography in the third. The differences in retinal artery pressures on the two sides in all 3 cases were significant and much greater than the range of differences in normal subjects. Retinal artery pressures and other data relating to these cases are given in Table 1. All measurements were made by the same observer (F.C.B.).

Case 1 (27353). R.E.B., a 65-year-old white male clerk, was admitted to the Veterans Administration Hospital, Iowa City on Nov. 20, 1956. He had been under care for arterial hypertension for 4 years but felt well until Nov. 6, 1956 when he noted loss of grip of the left hand and weakness of the arm. The following day the left arm was "useless." Later he experienced transitory numbness of the left side of the body, face and tongue. There were brief "jerking" spells beginning in the left hand and spreading to the arm, shoulder and leg with turning of the head to the right. There were no headaches or visual symptoms.

Examination. The patient was alert and oriented. The left arm hung at his side but the gait was normal. The brachial blood pressure was 220/110 mm. of Hg. The heart was moderately enlarged with a grade 2 systolic murmur. The chest was clear and abdomen was normal. The pulses in the legs were of poor amplitude. The common carotid pulses in the neck were normal. There was left facial palsy. The fundi displayed numerous superficial small hemorrhages, more on the right, and arteriolar

TABLE 1

Retinal artery pressures in patients with thrombotic occlusion of the internal carotid artery*

Case	Clinical Data	Retinal Artery Pressure in Grams				Brachial Arterial Pressure, mm. of Hg
		Presumed Normal Side	Occluded Side	Per Cent Difference		
				Systolic	Diastolic	
1. R.B. Age 65 Male	Slowly and intermittently increasing hemiparesis on left with focal seizures on left. Paralysis increased under observation. High internal carotid occlusion established at surgery. Diabetic	82/26 Left	42/12 Right	49	54	172/88
2. F.A. Age 61 Male	Stepwise progression of right hemiparesis and dysphasia—becoming stable. Occlusion of internal carotid above bulb relieved by intimectomy. Sudden increase in paralysis 5 hrs. after surgery. Propagating clot and possible embolism	86/44 Right	50/32 Left	42	27	158/90
3. F.K. Age 57 Female	Confusion, lethargy, slurred speech, right hemiparesis increasing in hospital. Occlusion of left internal carotid near origin found by angiography. (Readings 1 yr. after diagnosis established)	72/32 Right	50/24 Left	30	25	110/74 (previous average level)

* Intraocular pressures were within normal limits and essentially equal in the two eyes in all cases.

sclerosis. Strength of the left arm was reduced and grip was minimal. The right arm and both legs functioned well. He had hyperreflexia on the left without Babinski sign, and hypesthesia of the left hand.

Urinalysis revealed sugar, and elevated blood sugar readings confirmed the diagnosis of diabetes mellitus which was controlled with insulin and diet. Routine blood counts were normal. The blood VDRL and spinal fluid Kolmer tests were negative. Lumbar puncture disclosed a pressure of 160 mm. of water. The fluid was clear with 2 white blood cells/c.mm.; total protein was 40 mg. per cent. Roentgenograms of skull and chest were regarded as within normal limits except for left ventricular hypertrophy. Electrocardiogram showed minor ST and T wave changes.

Course. Five days after admission the left facial weakness worsened and the left upper extremity was barely moved. There were dizziness, weakness and drowsiness. The patient became bedridden. Electroencephalogram disclosed focal 4–5/sec. activity in the right temporal region. Retinal blood pressure studies done that day with brachial pressure of 172/88 mm. of Hg revealed pressures: O.D. 42/12 and O.S. 82/26 gm. With this finding of approximately 50 per cent reduction of pressures on the right, a presumptive diagnosis of occlusion of the right internal carotid artery was made.

Operation. On Nov. 26, 1956, under local anesthesia, the right cervical carotid system was exposed. There was some thickening of the wall of the common carotid artery but it and the external carotid were pulsating. The internal carotid artery

just above the bifurcation was thickened and firm with minimal pulsation and yellowish walls. The carotid bulb was opened after isolating this segment with clamps, and thickened intima, atherosclerotic plaques and a small fresh clot were removed. There was not complete obstruction at this level but when the clamp was removed from the internal carotid distal to the site of incision and intimectomy there was no back flow of blood. Catheter suction to a distance of 6 cm. from the bifurcation did not yield further clots.

Postoperative course was that of severe cerebral infarction. He manifested left facial palsy, absence of function of the left upper extremity and paresis but good movement in the spastic left lower extremity. There was left homonymous hemianopsia. He became oriented but displayed little initiative. Carotid and temporal pulses remained palpable. The retinal pressure readings showed no tendency to return to equal levels and, 11 weeks after surgery, were: O.D. 52/26 and O.S. 115/44 gm. Brachial blood pressure was 144/70 mm. of Hg at that time.

Discussion. The clinical course suggested the diagnosis of occlusion of the right internal carotid artery. The retinal artery blood pressure on this side was approximately 50 per cent lower in both systolic and diastolic readings than that on the left. Thus, substantial weight was added to the presumptive diagnosis. Angiography was not done. Direct exploration confirmed the presence of obstruction by failure to obtain back flow into the opened and proximally occluded internal carotid artery. Subsequent studies showed no tendency for retinal artery pressures to become equal. This has been the finding of Svien and Hollenhorst[20] in cases of spontaneous or surgical occlusion of the internal carotid artery.

Case 2 (28502). F.A., a 61-year-old white male machinist, was admitted to the Veterans Administration Hospital, Iowa City, Jan. 10, 1957. Six weeks before admission he awakened with weakness of the right hand and arm. This progressed and was soon followed by weakness of the right leg and later of the right face. He denied headaches, visual symptoms and difficulty with speech.

Examination. The patient was short, obese, moderately dysphasic but alert and cooperative. The gait was typical of hemiplegia. The fundi manifested arteriolar narrowing and a few old hemorrhages on the left. Brachial blood pressure was 160/90 mm. of Hg. The chest, heart and abdomen showed no abnormalities. The visual fields were full to confrontation. There was weakness of the right lower face. The right arm was paretic and grip was ineffective. The right leg was weak and spastic. There were hyperreflexia, Babinski sign and Hoffmann sign on this side.

Urine and blood were within normal limits. Blood serology was negative. Lumbar puncture disclosed a pressure of 160 mm. of water. The fluid was colorless with 8 white blood cells/c.mm. Total protein was 43 mg. per cent, and spinal fluid Kolmer was negative. Roentgenograms of skull and chest were normal. Electrocardiogram showed minor abnormalities of P and T waves. Electroencephalogram revealed focal 3–4/sec. waves in the left temporal region and low voltage over this hemisphere.

Because thrombotic occlusion of the left internal carotid artery was suspected, retinal artery blood pressures were determined. The readings were: O.D. 86/44; O.S. 62/26 gm. A few days later the readings were O.D. 86/52; O.S. 52/26 gm. The intraocular pressures were equal and normal. The clinical diagnosis seemed well supported. Examination the day before surgery revealed slight improvement of previous deficits. The carotid pulsations on the left as high as they could be palpated seemed less than on the right. Pulses in the temporal arteries were equal.

Operation. On Jan. 30, 1957, under local anesthesia, the left common carotid artery and its branches were exposed through an incision along the anterior border of the sternocleidomastoid muscle. The common and external carotid arteries pulsated strongly but their walls manifested atherosclerotic thickening. The carotid bifurcation was hard, irregular and not compressible. This density extended up a distance of 2–3 cm. into the internal carotid artery. No pulsation could be detected here or in the short segment of visible and relatively normal-appearing artery above. Arterial graft was considered but the difficulty in exposing the internal carotid sufficiently above the point of obstruction caused us to abandon this. An incision was made opening the common carotid artery and the bulb, and intimectomy and thrombo-endarterectomy were done in this area, removing the thick atherosclerotic lining of the bifurcation including the extensions of this into the

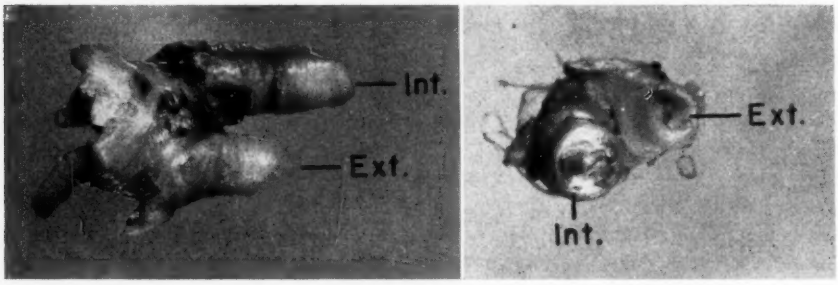

FIG. 1. *Case 2.* Photographs of intraluminal lesion removed in one piece (×1.4). It is a cast of the carotid bulb and proximal segments of the internal and external carotid arteries. The lumen of the external carotid is compromised by atherosclerotic changes but is patent. The internal carotid is completely occluded by an old organized thrombus at the periphery and more recent thrombus in the center.

external and internal carotid arteries. The lumen of the internal carotid artery had been completely occluded by old organized thrombus and a small recent clot. The specimen was removed in one piece (Fig. 1). A free back flow of blood was obtained from the internal carotid artery and the arterial incision was closed. When the clamps were released the entire system pulsated strongly.

Just before surgery the brachial blood pressure was 158/90 mm. of Hg. The retinal pressures were: O.D. 86/44; O.S. 50/32 gm. When the left external carotid was clamped the pressure on the left dropped to 30/14 and when the clamp was released two further immediate measurements were: 20/8, then 42/18 gm. O.S.

Course. The patient showed no immediate ill effects from the operation and retinal artery pressures in 2 hours were: O.D. 86/40 and O.S. 76/40 gm., seeming to indicate restoration of carotid flow on the left. Approximately 5 hours after surgery the patient was found to be aphasic and hemianopic on the right. Movements of right arm and leg were much reduced. The left temporal artery was pulsating. A postoperative thrombosis or embolism was suspected and the wound was opened. The common and external carotid arteries were pulsating normally. From its origin and for a distance of about 3 cm. the thin-walled internal carotid was darkened and distended by a fresh thrombus. The arterial incision was opened, clot was removed and an attempt was made to suck out propagated clot above. This was partially successful but a rather poor back flow was obtained. Stellate ganglion block was done. The next day retinal pressures were: O.D. 84/40; O.S. 46/32 gm. Brachial pressure was 130/70 mm. of Hg.

The patient followed a typical course of severe cerebral infarction with some minor improvement in speech but none in the use of the arm. The leg could be moved weakly.

The last observation of retinal artery pressures was on Feb. 27, 1957. The readings were: O.D. 80/42; O.S. 60/30 gm.

Discussion. The clinical course and findings suggested the possibility of internal carotid occlusion on the left and several readings of retinal artery pressures on this side were significantly lower than those on the right. Palpation of the neck was not especially helpful in diagnosis. Angiography was not done.

There was complete occlusion of the left internal carotid artery and partial occlusion of the bulb and external carotid artery. Since a vessel graft seemed impossible because of difficulty in exposing the artery, intimectomy and thrombo-endarterectomy were done. Experience in vascular surgery elsewhere suggests that intimectomy in vessels of this size is often followed by intravascular clotting. Such was the case here, and propagating thrombus or embolus was responsible for the unfortunate outcome. The possibility of mobilizing the cervical carotid system sufficiently to anastomose common to internal carotid artery after resection of the bulb and a portion of the internal carotid artery has been demonstrated.[9,18]

The only observation of nearly equal retinal artery pressures in the two eyes was during the few hours following relief of arterial obstruction and before postoperative intravascular clotting occurred. The further drop in retinal artery pressure from 50/32 to 30/14 gm. on the left when the left *external* carotid artery was clamped deserves comment. This vessel was apparently carrying significant anastomotic blood flow to the ipsilateral ophthalmic artery. Was this flow significant in respect to the needs of the cerebral hemisphere on this side?[24] It apparently did not prevent some degree of ischemia and infarction. Nor did occlusion of the external carotid artery cause any immediate increase in neurologic deficits. Miletti[15] has pointed out that digital compression of the common carotid artery on the side of occlusion of the internal carotid artery does not produce the fall in retinal artery pressure that is expected in a normal system. This maneuver was not carried out here or in our other patients but it seems likely that it would have caused a further drop in pressure in this case.

It is quite possible that when the neurologic status of the patient with carotid occlusion is stable or slowly improving he is no longer a candidate for surgery. The few gratifying results so far reported have resulted from relief of obstruction during the period of vacillating function of the involved hemisphere.

Case 3 (S.U.I. 56–1130).* F.K., a 57-year-old white female, was admitted to the State University of Iowa Hospitals Jan. 24, 1956. Complete history was not available. Disorientation had been noted by her physician 3 weeks before. The blood and

* The authors wish to express their appreciation to George Perret, M.D. and Arthur Eisenbrey, M.D. of the Neurosurgical Service, State University of Iowa Hospitals for permission to include this case.

spinal fluid Kolmer were found to be positive with elevation of gold curve. Penicillin in total dosage of 12,000,000 units was given.

Examination. The patient was lethargic and disoriented. Speech was slurred. Simple commands were carried out. Brachial blood pressure was 116/65 mm. of Hg. The chest was clear, and there was a grade 1 systolic murmur. Peripheral pulses were of good quality and carotid pulses were present. There was right hemiparesis, more evident in face and arm, with hyperactive reflexes and Babinski sign on this side. Retinal vessels were sclerotic. Visual field determination could not be accomplished.

Routine laboratory studies showed a mild hypochromic anemia. Blood and spinal fluid Kolmer were positive. Lumbar puncture revealed a pressure of 110 mm. of water. The fluid was colorless. There were 5 white blood cells/c.mm. and total protein was 61 mg. per cent. Fasting blood sugar and blood urea nitrogen levels were normal. Roentgenograms of skull and chest were within normal limits. Electroencephalogram revealed focal slow activity in the left frontotemporal region.

Course. Confusion and lethargy continued. There was persistent headache in the left temporal region. Thrombosis of the internal carotid artery was considered as was neurolues and cerebral tumor. Determination of retinal artery pressures was attempted but the patient could not cooperate. The hemiparesis progressed and ventriculography done on Feb. 3, 1956 revealed slight ventricular dilatation. On February 16 bilateral percutaneous carotid angiography was done. There was obstruction of the left internal carotid artery just beyond its origin. Injection of dye on the right side resulted in bilateral filling of middle and anterior cerebral arteries. Unfortunately there was a subsequent marked increase of the hemiparesis and nearly complete aphasia. Stellate ganglion blocks were done. The right arm remained flaccid but the patient eventually could walk. Speech was unintelligible. No gross visual field defect was evident.

At her last visit on Feb. 20, 1957, the patient was ambulatory with hemiparetic gait. Dysphasia was marked. The right arm was flaccid and hypesthetic.

Ocular pressure was normal and equal on the two sides. The retinal artery pressures were: O.D. 72/32; O.S. 50/24 gm.

Discussion. A question that might have been raised in this case is whether the demonstrated occlusion of the left internal carotid artery was responsible for the signs and symptoms. This point has been raised before.[11] It seems quite likely that occlusion of the internal carotid artery causes a sufficient deficit in blood pressure and blood flow to endanger function if occlusive disease exists in the intrinsic blood vessels of the brain or in the other arteries supplying the brain or if collateral circulation is defective. The vascular deficiency might also unfavorably influence the course of a coexisting disease. Diminished blood flow and pressure based on lowered cardiac output and systemic circulatory changes would be much more serious so far as nutrition and oxygenation of the brain is concerned if a major vascular path to the brain were obstructed.[7]

The case is more immediately in point in demonstrating a significantly lower retinal artery pressure on the side of the carotid obstruction one year after onset of disability and discovery of the occlusion. It also calls attention to the necessity for cooperation of the patient in measuring retinal artery pressures.

Ventriculography might well have been indicated even though a difference in retinal artery pressures could have been demonstrated. However, many case reports would suggest that patients who demonstrate a more typical syndrome of vascular insufficiency could be spared air studies if the clinician had knowledge of lowered retinal artery pressure on the involved side.

The case emphasizes the hazard of angiography in the patent carotid when the other is obstructed.[13] It seems quite possible that the hemisphere in which blood pressure, and presumably blood flow, is deficient is more vulnerable to the deleterious effects of this procedure. Knowledge of significant difference in retinal artery pressures in the two eyes should make the surgeon aware that the *carotid system ipsilateral to the lower pressure may be partially or completely occluded.*

Contralateral compression of the cervical carotid artery is often practised during angiography. It is potentially dangerous when an obstruction already exists in the carotid to be injected. This inadvertence could be avoided with knowledge of retinal artery pressures pre-operatively. The performance of angiography only on the side of suspected occlusion or brain disease may result in failure to recognize bilateral occlusion of the internal carotid arteries, but this condition is quite uncommon. Diminished carotid and retinal artery blood pressure may be contemporaneous with independent disease of the brain.

COMMENT

We do not intend to imply that a presumably occluded cervical carotid system should always be explored directly before percutaneous angiography.* However, when a patient presents symptoms appropriate to internal carotid thrombosis and a significant lowering of retinal artery pressure on the side of the lesion, direct exploration without preliminary percutaneous angiography may prove to be the best judgment. This has been suggested in effect by Schneider and Lemmen[17] in the management of traumatic internal carotid thrombosis. They believe that in this circumstance open angiography can be performed more reliably than can percutaneous angiography. In addition, it gives opportunity for direct inspection of the area of trauma. Much the same argument could be given for direct exploration in the cases of spontaneous carotid occlusion. Open angiography could be done if an occlusive lesion were not disclosed at operation. Boldrey *et al.*[3] recommended open angiography in their report of 24 cases of angiographically demonstrated internal carotid thrombosis. The open method permits inspection of the vessel walls and assures proper placement of the needle. Since time is of importance in these cases and since most carotid occlusions are segmental and near the bifurcation the argument would seem to be supported. However, symptom-producing obstructions may not be complete and information as to this matter is of importance in preparing for operation. If occlusion is complete, the surgeon may take his time in arterial resection and anastomo-

* The use of anticoagulants in syndromes of impending cerebral infarction is not within the scope of this study.

sis,[9,18] intimectomy[5,19] or vessel graft[6] without fear that while so doing he is increasing cerebral ischemia. This is not the case in partial obstructions. Here some expedition in surgery, artificial arterial by-passes[5] and/or hypothermia[10] may be in order. Retinal artery pressures could not be relied upon to distinguish partial from complete occlusion although angiography could do so.[12] However, if digital compression of the common carotid artery caused a further decrease in an already lowered ipsilateral retinal pressure then a partial occlusion might be suspected (see discussion of Case 2). A significant residual flow in a partially obstructed carotid system could be detected at exploration. If the operation were performed under local anesthesia the patient's ability to tolerate complete occlusion could then be tested. The Matas test done pre-operatively might give this same information and perhaps should cautiously be done as a routine.

It is possible that abnormalities of arterial supply of the brain, as well as intracranial masses that interfere with circulation, may be a source of error in interpretation of the meaning of differences in readings of retinal artery pressure. A finding of unilateral abnormally elevated retinal artery pressure has been recorded in a case of intracranial tumor, the latter being on the side opposite the higher pressures.[8] In cranial arteritis the ophthalmic artery may be severely involved with or without evidence of cerebral ischemia. Retinal artery pressures might be quite low in this condition with no corresponding reduction in carotid flow.

SUMMARY

An approximation of retinal artery blood pressure can be made by the technique of ophthalmodynamometry. The measurements so obtained directly reflect the pressure in the internal carotid artery and are of definite value in comparing the pressures in these arteries on the two sides.

Comparative studies of retinal artery pressure in 3 cases of proven occlusion of the internal carotid artery revealed that pressures on the side of occlusion were lower than those on the contralateral side by 30 to 49 per cent in systolic and 25 to 54 per cent in diastolic readings. Two of the 3 patients were subjected to surgery without preliminary angiography and in these the measurements of retinal artery pressure proved to have given substantial and valid support to the clinical diagnosis.

In the 2 cases in which the carotid system was explored, the obstruction in one was above the limits of cervical approach to the vessel. In the other satisfactory relief of obstruction was provided by thrombo-endarterectomy. Evidence of re-establishment of circulation by direct inspection was accompanied by an increase in retinal artery blood pressure on the same side. Early intravascular clotting and possible embolism vitiated the immediate success and disability was increased.

Surgery of vascular occlusion of the internal carotid artery in the neck is still in an investigative stage. Advances in vascular surgery generally are likely to promote considerable effort toward an attack on the diseased carotid system. Determination of retinal artery pressures is a simple, safe

and valuable aid to diagnosis of occlusive vascular disease of the carotid system. It promises, as well, to be of value in directing the best use of angiography.

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EVALUATION OF ROENTGEN CONTRAST AGENTS USED IN CEREBRAL ARTERIOGRAPHY

I. A SIMPLE SCREENING METHOD*

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SEVERAL techniques for testing the effects of roentgen contrast media upon the central nervous system have been used. In these studies the brain has been used as the site of the test, with injury to the blood-brain barrier being the most widely employed index of a toxic action.[1–7] It has been generally recognized that seizure discharges are provoked by toxic concentrations of these agents, and, consequently, electroencephalographic changes have also been employed as indicators of injury.[2,3,8] Most experiments have been designed as acute studies, with attention focused upon the immediate and early phases of the injury. It has been observed, however, that, if the experiments are prolonged for several hours, early parenchymal changes also appear.[3,7] Recent studies have indicated that the spinal cord, an area of injury allowing extended survival of the experimental animals, can be used as a site of the test.[12] This choice of a testing area would allow the use of such absolute and measurable criteria of toxicity as alterations in function and structure of the affected tissues to supplement or replace the established indices. The present report describes a method of testing roentgen contrast media, developed on the basis of the above considerations.

METHOD

Theoretically, the toxic effects of contrast media may be tested on the basis of three variables, namely: concentration, total dosage, and iodine content. Past studies in these laboratories[3] have, however, demonstrated that toxic effects of contrast agents bear no relation to their iodine content. Accordingly, the standard approach used is an evaluation of the effects of the highest commonly used concentrations of an agent. For this concentration, the dosage is titrated on the basis of a cc. per kg. of body weight until the maximal nontoxic level is established. In a second testing procedure, a fixed volume of the contrast medium is used, and the concentration is varied until the maximal nontoxic dosage is found.

The test is a simplification and standardization of the method of Margolis, Tarazi and Grimson.[12,14]

* This study was supported by a research grant (B 1102 and G 869) from the National Institutes of Health and by a research grant from the National Paraplegic Foundation.

Test substances are introduced through a catheter inserted into the femoral artery and passed retrograde into the abdominal aorta to the level of the 3rd lumbar vertebra of adult dogs. The test dose is injected manually at the rate of approximately 5 cc. per sec. with the animal in the supine position. The supine position is used because of observations that contrast media injected in this manner exert a more toxic effect upon the cord,[12,14] presumably because of the gravitational effect upon flow of the heavy radiopaque material. The injection of contrast media at this rate causes a retrograde filling of the aorta above the tip of the catheter for a distance of 3 to 5 cm. (Fig. 1). Observations of the immediate effect, the condition of the animal upon recovery from anesthesia, and the daily post-injection status are made. Animals are sacrificed after 4 to 6 days. The entire spinal cord is removed, placed in a fixative consisting of isotonic neutral formalin, and later sectioned transversely at 0.3 to 0.5 cm. intervals. After the gross features have been recorded representative sections are chosen for microscopic study. Paraffin embedding is used routinely, with selected sections being embedded in celloidin. The histologic techniques employed include hematoxylin-eosin, the Klüver-Barrera stain,[10] and a modification[11] of this method using the periodic acid-Schiff reaction and hematoxylin, producing a combined picture of the myelin pattern, the cell picture, and the vascular bed.

FIG. 1. Lateral roentgenogram taken 0.5 second after beginning of the injection of contrast media (Hypaque—70%) into the abdominal aorta to illustrate retrograde filling. Tip of catheter is at site shown by arrow.

CRITERIA OF TOXICITY

Three indicators are used to measure the toxicity of the injected agents: 1) the immediate convulsive response; 2) neurological deficit; and 3) anatomic lesions. All these have been described previously,[12,14] but are presented here in a more detailed form, modified on the basis of further observations to allow a ready classification of the effects into categories of progressive severity.

The immediate convulsive effects are graded as follows:

None— No reaction is recognized.

Mild— There is a momentary feeble dorsiflexion of the trunk and/or hind legs, or a brief extension of the tail. This reaction, as well as the other toxic reactions, is accompanied by an acceleration and deepening of respira-

tion. It is not followed by signs of abnormal irritability or reflex changes in the animal.

Moderate—This is a brief, but definite convulsion involving the trunk, rear limbs and tail. This reaction is characterized by a sequence of immediate brief dorsiflexion, a tonic phase lasting for 1 minute or less, and a clonic phase of approximately the same duration. There follows a 2- to 5-minute period of hyperirritability during which clonus may be elicited by tactile stimuli.

Severe— This reaction begins with an immediate strong dorsiflexion which is quickly replaced by a severe extensor rigor, involving the trunk, hind limbs, and tail. The tonic phase persists for 1 to 2 minutes, and is followed by a longer period of clonus. The clonic contractions may persist for as long as 30 minutes, but usually subside within 5 minutes. The clonic phase is then followed by a 5- to 30-minute period of hyperirritability. Other manifestations of this severe toxic reaction may include whimpering of the anesthetized animal and loss of sphincter control.

The neurological deficit is graded as follows:

None— No alteration of function is observed.

Mild— A mild paresis of the hind legs is produced, which is not apparent until the animal is exercised. This usually clears over the course of 3 to 5 days.

Moderate—Paraparesis is more marked than above, but it is not incompatible with locomotion.

Severe— A paraplegia, usually spastic, but sometimes flaccid, is present.

Sensory losses, which are more difficult to evaluate in animals, are not used as indices of toxic action.

The anatomic lesions are graded as follows:

0: No lesions are demonstrable.

1: There are sparsely scattered microscopic foci of destruction, affecting gray or white matter, present in one or more sections of spinal cord. In some cords only a focal or diffuse glial hyperplasia within the gray substance is observed.

2: There are multiple small (1–2 mm.) scattered foci of destruction of gray matter, with or without involvement of white matter or spinal nerve roots, distributed over 5–10 cm. of spinal cord.

3: Extensive focal discrete or confluent zones of destruction of gray matter, with or without involvement of white matter or spinal nerve roots, extending over 5–10 cm. of spinal cord, are present.

4: Complete, or nearly complete, devastation of gray matter, with or without involvement of white matter or spinal nerve roots, involving from 10 to 18 cm. of cord, is observed.

5: There is complete, or essentially complete, transverse necrosis of the spinal cord, often with extensive destruction of spinal nerve roots, involving from 10 to 18 cm. of cord.

For clarity of presentation these lesions are represented here in a diagrammatic form (Fig. 2). The more severe grades of these injuries are shown in illustrations recorded elsewhere: Grade 3 in Fig. 4B;[12] grade 4 in Figs. 1A, 1B, 2A, 2B, and 4A;[12] grade 5 in Fig. 6B[12] and Fig. 2B.[14]

The plan for the grading of the criteria of injury used in these studies is

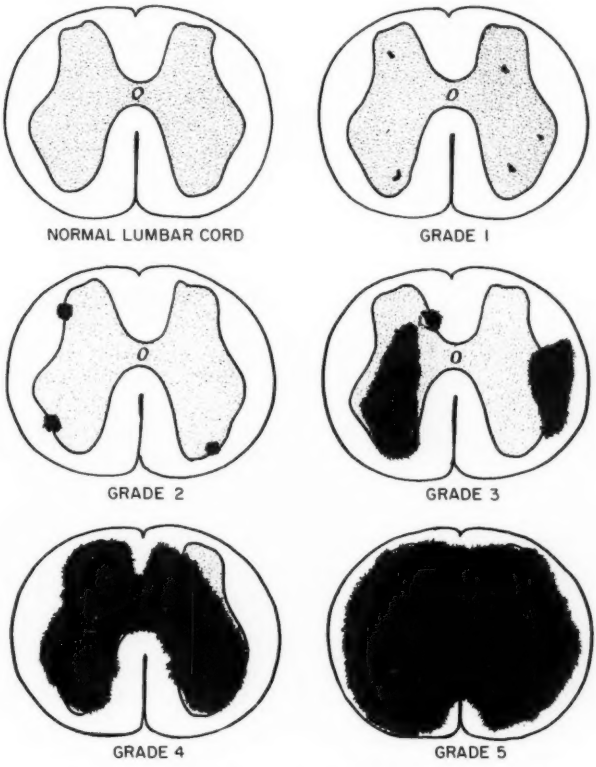

FIG. 2. Drawings showing system for grading anatomic lesions. The blackened areas indicate the extent of destruction of the lumbosacral area of the spinal cord.

the result of observations made upon approximately 250 animals. The general correlation of these three indices, followed closely by all but a few dogs, is presented in Table 1. It must be emphasized, however, that the progression in severity of all of these criteria is nonlinear. With each there is a wide gulf between the reactions graded as mild or moderate, and those rated as severe. This broad gap is illustrated by Fig. 3 which shows the relationship between a quantitative index of the cord injury and the grade of the anatomic lesion. This index has been constructed by making the assumption that with each injury an equal length of cord has been involved, and that in the five grades of injury 1, 5, 30, 70, and 90 per cent respectively, of the cord parenchyma has been destroyed. This allows the extent of the cord lesion to be expressed either as a percentage or as a proportional value. Because both the extent and the intensity of the lower-grade lesions have been exaggerated in this index, the actual progression of the severity of injury from grade 2 to 3 is even more abrupt. Since the toxic action is focused primarily upon

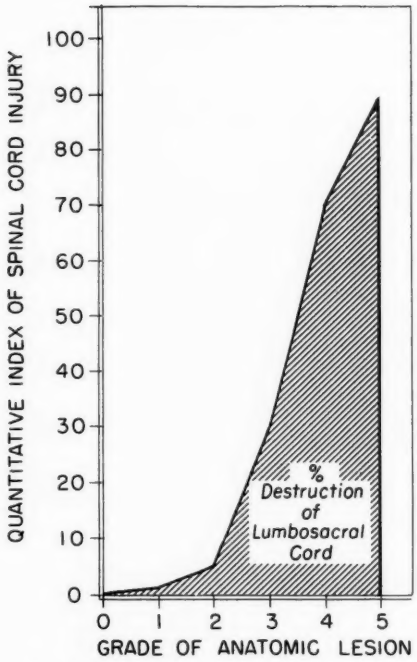

FIG. 3. Relationship of quantitative index of spinal cord injury to grade of anatomic lesion.

gray matter and minimal injuries are masked in functional studies, a hypothetical curve showing the progression in severity of the residual disability of animals would rise even more sharply between lesions of grade 2 and 3.

DISCUSSION

In recommending the cord as the site of test for roentgen contrast media, Margolis *et al*[12] referred to several factors favoring its use. There is a close correspondence in structure and blood supply of the cord of the dog, the animal chosen for these tests, and of man. The greater susceptibility of the canine cord to injury by the contrast medium is the result of its low anatomical position, rather than an intrinsic difference in vulnerability. The caudal position of the canine cord renders it readily accessible to agents injected into the aorta, making this test a most simple and dependable procedure. Finally, the site of injury allows an extended survival of the experimental animal and the full evolution of the contrast medium lesion.

While disturbed permeability remains one of the most sensitive indicators of injury, it is probable that this disorder has an extremely variable duration in the case of contrast medium injury. In a group of apparently reversible injuries to the blood-brain barrier produced by Broman and associates[4] the defect persisted for but a few hours, and after contrast medium injury its duration was less than 2 hours. But when irreversible or necrotizing lesions were produced, the disorder lasted for 5 to 7 days. Only one reported study[9] has used changes in permeability as an index of injury to the

TABLE 1

Expected correlation of criteria of toxicity

Convulsive Effect	Neurologic Impairment	Anatomic Lesion (Grade)
None	None	0
Mild	None or mild	1
Moderate	Mild to moderate	2
Moderate to severe	Moderate to severe	3
Severe	Severe	4
Severe	Severe	5

spinal cord by contrast media. These experiments, which were of extremely short duration, also correlated a convulsive effect with injury. In a closely correlated study of injury to the spinal cord by contrast media, we have repeatedly observed breaks in the blood-brain barrier accompanying toxic reactions. However, our evaluation experiments have not stressed alterations of the vascular barrier, primarily because the value of this change as a quantitative test in studies of extended duration is doubtful. Seizure discharges attending the contrast medium injury act as an immediate and sensitive indicator of a toxic action, which may be observed visually or recorded by electroencephalograms. Further, these changes are classifiable and are relatively longlasting.[2,3,8] The neurologic deficit and the anatomic lesions in the cord, the two criteria of injury added by our spinal cord studies, are alterations of permanent character, subject to more accurate quantitative analysis than the established indices of toxicity.

The simplicity of this suggested testing method is one of the strongest factors favoring its use. It does not require a painstaking carotid dissection, nor the choice between an open surgical or a blind needle approach to the abdominal aorta. The point of catheterization, the femoral artery, is distally placed so that thrombotic, embolic, hemorrhagic, or necrotizing complications of the catheterization procedure cannot possibly affect the circulation to the central nervous system. Further, the substance reaching the spinal cord is a mixture of blood with the injected agent, a condition which is directly comparable to the situation in clinical arteriography. It is evident that the actual concentration of the contrast agent reaching the central nervous system must remain unknown with this technique. For such information a method in which the injection is made into the carotid circulation with the artery occluded proximally and with the external carotid ligated is most satisfactory.[2,3] However, indirect information concerning the degree of dilution may be obtained by comparing the concentrations of Urokon which are toxic for the brain and spinal cord, both of which appear to be equally susceptible to injury by this agent.[12] Large doses of this substance injected into the carotid artery of dogs[13,16] and rabbits,[2,3] presumably minimally diluted, are clearly toxic for the brain in a 30 per cent concentration, with a sharp decrease in toxicity at concentrations of 25 per cent or less.[13] Our own studies[15] have demonstrated that Urokon, injected into the canine aorta of supinely positioned dogs in 1 cc. per kg. doses is toxic at 70 and 60 per cent, irregularly, but sometimes highly toxic at 50 per cent, and nontoxic at 40 per cent concentrations. A dilution of this agent to between 50 and 60 per cent of its original concentration (i.e. 50 per cent diluted to 25 or 30 per cent) during transit from the aorta to the spinal cord may be assumed from these comparative studies. Parenthetically, the fact that 70 per cent Urokon is rarely toxic to the cord when injected with the animal prone could be readily explained by a dilution to between 30 and 45 per cent of its original concentration (i.e. 70 per cent diluted to 20 to 31.5 per cent) in the passage from aorta to cord.

In addition to using this technique as a simple method of screening and comparing roentgen contrast agents, the investigator may elaborate these

tests at will without altering the basic method. For example, the effects of the agents under evaluation upon blood pressure, respiration and heart rate may be studied. And in the same tests the quality of roentgen contrast provided by the established safe dosage level for each substance tested may be assessed. Finally, the determinate character of the criteria of toxicity provides ready standards for comparison in tests exploring a means of modifying the severity of these toxic effects. In the paper to follow,[15] the application of this method in the testing of five roentgen contrast agents will be described.

SUMMARY

A simple method for evaluating the toxicity of contrast media upon the central nervous system has been described. The method employs the spinal cord of the dog as the site of the test and uses the immediate convulsive effect, the residual neurological deficit, and the resultant anatomic changes in the parenchyma of the cord as the criteria of injury.

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EVALUATION OF ROENTGEN CONTRAST AGENTS USED IN CEREBRAL ARTERIOGRAPHY

II. APPLICATION OF A NEW METHOD*

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A NEW method for evaluating the toxicity of roentgen contrast media has been described in the preceding paper.[4] This testing method, which employs the spinal cord of the dog as the site of the test, uses the following criteria as indices of toxicity: the immediate convulsive effect, the residual neurological deficit, and the resultant anatomic changes in the spinal cord. The application of this method to a comparative study of five contrast media is presented in the present report.

EXPERIMENTAL

The contrast media tested in this study included Diodrast, Hypaque, Urokon, Miokon, and Renografin.† The structural formula of each of these agents is shown in Fig. 1. The basic molecule of Hypaque and Renografin is identical, the only difference between these two agents being the relative proportion of sodium and methylglucamine diatrizoate contained in each.[3,6] The methylglucamine radical has been added to these compounds in order to increase their solubility.[6] It is also present in the 90 per cent solution of Miokon, or sodium diprotrizoate. The absolute per cent of the sodium and methylglucamine salts in Hypaque,[6] Renografin,[3] and Miokon is shown in Table 1. The 70 per cent concentration of Hypaque and Miokon used in the present study was obtained by mixing equal volumes of the 50 and 90 per cent solutions. The 70 per cent concentration of Renografin was obtained by mixing equal parts of the 60 and 85 per cent solutions and adding an appropriate quantity of distilled water.

These tests followed the methods presented in detail in the preceding paper.[4] The basic plan of the study called first for an evaluation of each agent in a 70 per cent concentration at doses of 1 cc. per kg. When a compound was found to be highly toxic the total dose at this concentration was halved, or the agent was tested in progressively decreasing concentrations, holding the total volume of the injection at 1 cc. per kg., until a non-

* This study was supported by a research grant (B 1102 and G 869) from the National Institutes of Health and by a research grant from the National Paraplegic Foundation.

† The contrast media were kindly furnished in generous quantities by the following: Winthrop Laboratories, Inc., New York, N.Y. (Diodrast and Hypaque); Mallinckrodt Chemical Works, St. Louis, Missouri (Urokon and Miokon); and E. R. Squibb and Sons, New York, N.Y. (Renografin).

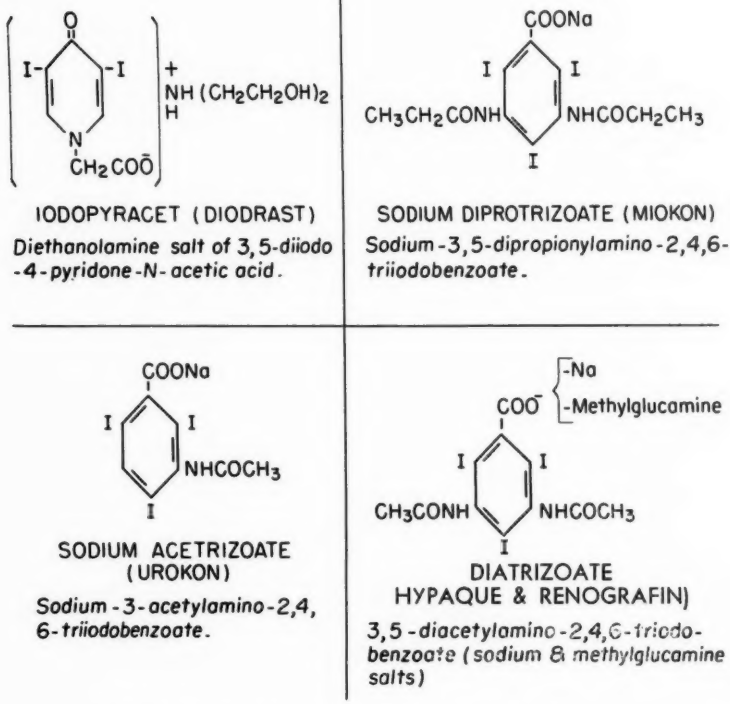

FIG. 1. Structural formula of contrast media used in this study.

TABLE 1

Proportion of sodium and methylglucamine salts in Hypaque, Renografin, and Miokon

Contrast Agent	Concentration Per Cent w/v	Absolute Per Cent (w/v) of Sodium and Methylglucamine Salt in Each Agent	
		Sodium Salt	Methylglucamine Salt
Hypaque (diatrizoate)	50	50	0
	70	40	30
	90	30	60
Renografin (diatrizoate)	60	8	52
	70	4.5	65.5
	76	10	66
	85	0	85
Miokon (diprotrizoate)	50	50	0
	70	40	30
	90	30	60

TABLE 2

Summary of evaluation tests of five roentgen contrast agents in 79 dogs

Agent	Dose, cc./kg.	Concentration (Per Cent) of Agent and Number of Animals Tested			
		30	40	50	70
Urokon	0.5				5
	1.0	4	5	5	14*
Diodrast	1.0				5
	2.0				5
Hypaque	1.0				5
	2.0				5
	3.0				5
Miokon	1.0				5
	2.0				6
Renografin	1.0				5
	3.0				5

* 8 animals injected in prone position.

toxic level was reached. When a compound was found to be relatively innocuous the dose was doubled or trebled until a definite toxic level of the concentrated (70 per cent) agent was found. A summary of these evaluation studies is presented in Table 2, which also lists a few other variations of the testing procedure. All compounds were kept sealed and protected from light until ready for injection. Various factors such as the care and handling of the animals, the temperature of the injected media, and the operative technic were closely controlled.

RESULTS

Urokon. The tests of this agent, evaluated in 33 dogs, are summarized in Table 3. In a 70 per cent concentration this compound exerted a severe toxic effect at both 1.0 and 0.5 cc. per kg. doses. When this volume dose was kept at 1 cc. per kg. and the concentration of the agent was reduced, severe toxic effects were encountered in 2 of 5 animals injected with 50 per cent solution, and it was not until the concentration was reduced to 40 per cent that a significant reduction in toxicity was consistently observed. The animals receiving the 30 per cent concentration in a 1 cc. per kg. dosage showed no toxic effects. The influence of posture upon the toxic action of this agent is illustrated by the protective effect in 8 dogs injected in the prone position.

Diodrast. A summary of the tests on 10 dogs with this agent is presented in Table 4. In doses of 1 cc. per kg. the 70 per cent concentration of this medium produced a low order of toxic effect, manifested by a mild convulsive response and a low-grade anatomic lesion, but without recognizable

TABLE 3

Summary of toxic effects produced by retrograde intra-aortic injection of Urokon (33 dogs)

Animal Number	Position	Conc. %	Dosage, cc./kg.	Convulsive Effect	Neurologic Impairment	Anatomic Lesion
1	Supine	70	1.0	Severe	Severe	3
2	Supine	70	1.0	Severe	Severe	4
3	Supine	70	1.0	Severe	Severe	3
4	Supine	70	1.0	Severe	Severe	5
5	Supine	70	1.0	Severe	Severe	5
6	Supine	70	1.0	Severe	Severe	5
7	Supine	70	0.5	Moderate	Mild	2
8	Supine	70	0.5	Severe	Severe	4
9	Supine	70	0.5	Moderate	Severe	5
10	Supine	70	0.5	Severe	Severe	3
11	Supine	70	0.5	Severe	Mild	1
12	Prone	70	1.0	Moderate	Severe	3
13	Prone	70	1.0	Mild	None	0
14	Prone	70	1.0	Moderate	Mild	1
15	Prone	70	1.0	Mild	None	0
16	Prone	70	1.0	Mild	None	0
17	Prone	70	1.0	Moderate	Moderate	1
18	Prone	70	1.0	None	None	1
19	Prone	70	1.0	None	None	1
20	Supine	50	1.0	Severe	Severe	5
21	Supine	50	1.0	Severe	Severe	5
22	Supine	50	1.0	Mild	None	1
23	Supine	50	1.0	Mild	None	0
24	Supine	50	1.0	Mild	Mild	2
25	Supine	40	1.0	None	None	0
26	Supine	40	1.0	Mild	None	1
27	Supine	40	1.0	Mild	None	1
28	Supine	40	1.0	None	None	0
29	Supine	40	1.0	Mild	None	0
30	Supine	30	1.0	None	None	0
31	Supine	30	1.0	None	None	0
32	Supine	30	1.0	None	None	0
33	Supine	30	1.0	None	None	0

TABLE 4

Summary of toxic effects produced by retrograde intra-aortic injection of Diodrast with animals in supine position (10 dogs)

Animal Number	Conc. %	Dose, cc./kg.	Convulsive Effect	Neurologic Impairment	Anatomic Lesion (Grade)
34	70	1.0	none	none	1
35	70	1.0	mild	none	1
36	70	1.0	moderate	none	2
37	70	1.0	mild	none	1
38	70	1.0	mild	none	2
39	70	2.0	mild	none	1
40	70	2.0	mild	mild	2
41	70	2.0	none	mild	1
42	70	2.0	moderate	mild	2
43	70	2.0	mild	mild	2

TABLE 5

Summary of toxic effects produced by retrograde intra-aortic injection of Miokon with animals in supine position (11 dogs)

Animal Number	Conc. %	Dosage, cc./kg.	Convulsive Effect	Neurologic Impairment	Anatomic Lesion (Grade)
44	70	1.0	none	none	0
45	70	1.0	none	none	0
46	70	1.0	mild	none	1
47	70	1.0	none	none	0
48	70	1.0	mild	none	2
49	70	2.0	mild	none	1
50	70	2.0	mild	severe	3
51	70	2.0	moderate	moderate	2
52	70	2.0	mild	mild	1
53	70	2.0	mild	none	2
54	70	2.0	mild	none	2

neurologic impairment. At 2 cc. per kg. the 70 per cent preparation produced a mild neurologic impairment, without a significant increase in the convulsive action or the grade of anatomic lesion.

Miokon. The results of the tests on 11 dogs with this substance are summarized in Table 5. At 1 cc. per kg. the 70 per cent solution produced inconsistent and borderline toxic effects, without recognizable neurologic impairment in the injured animals. At 2 cc. per kg. the 70 per cent concentration was consistently toxic, but severe injury was observed in but 1 of 6 animals. In addition to parenchymal injury a degeneration of isolated fibers in the spinal nerve roots of the lumbosacral cord was demonstrated in 8 dogs. The parenchymal injury was the predominant lesion in these animals, however.

TABLE 6

Summary of toxic effects produced by retrograde intra-aortic injection of Hypaque with animals in supine position (15 dogs)

Animal Number	Conc. %	Dosage, cc./kg.	Convulsive Effect	Neurologic Impairment	Anatomic Lesion (Grade)
55	70	1.0	none	none	0
56	70	1.0	none	none	0
57	70	1.0	none	none	0
58	70	1.0	mild	none	0
59	70	1.0	none	none	0
60	70	2.0	mild	none	1
61	70	2.0	mild	none	1
62	70	2.0	none	none	1
63	70	2.0	mild	none	1
64	70	2.0	none	none	1
65	70	3.0	mild	none	1
66	70	3.0	moderate	none	1
67	70	3.0	mild	none	1
68	70	3.0	mild	none	0
69	70	3.0	none	none	1

TABLE 7

Summary of toxic effects produced by retrograde intra-aortic injection of Renografin with animals in supine position (10 dogs)

Animal Number	Conc. %	Dosage, cc./kg.	Convulsive Effect	Neurologic Impairment	Anatomic Lesion (Grade)
70	70	1.0	none	none	1
71	70	1.0	mild	none	1
72	70	1.0	mild	none	1
73	70	1.0	mild	none	0
74	70	1.0	mild	none	1
75	70	3.0	mild	none	1
76	70	3.0	none	none	1
77	70	3.0	mild	none	0
78	70	3.0	none	none	1
79	70	3.0	mild	none	1

Hypaque. The results of tests on 15 dogs with this compound are shown in Table 6. The 1 cc. per kg. dose of the 70 per cent concentration produced no residual toxic effects. When the dose of this concentration was doubled and trebled minimal toxic effects were observed, without recognizable functional impairment in the injured animals. Rare degenerating fibers in the spinal nerve roots were noted in 9 dogs. In all but one animal (dog No. 65), these were the only anatomic changes noted.

Renografin. The tests of this agent in 10 animals are summarized in Table 7. At both 1 cc. and 3 cc. per kg. dose levels the 70 per cent concentration produced a mild convulsive response and a grade 1 anatomic lesion in most animals tested, without recognizable residual neurologic impairment. Scattered degenerating spinal root fibers were found in 3 dogs. In this series, however, parenchymal lesions were the predominant feature.

TABLE 8

Summary of toxic effects produced by retrograde intra-aortic injection of contrast media (includes dogs in supine position only)

Agent	Conc. % w/v	Dose, cc./kg.	Number Animals	Criteria of Injury and Number of Animals													
				Immediate Convulsive Response (Grade)				Neurologic Impairment (Grade)				Anatomic Lesion (Grade)					
				None	Mild	Mod.	Severe	None	Mild	Mod.	Severe	0	1	2	3	4	5
Urokon	70	0.5	5			2	3		2		3		1	1	1	1	1
		1.0	6				6				6				2	1	3
Diodrast	70	1.0	5	1	3	1		5					3	2			
		2.0	5	1	3	1		1	4				2	3			
Miokon	70	1.0	5	3	2			5				3	1	1			
		2.0	6		5	1		3	1	1	1		2	3	1		
Hypaque	70	1.0	5	4	1			5				5					
		2.0	5	2	3			5					5				
		3.0	5	1	3	1		5				1	4				
Renografin	70	1.0	5	1	4			5				1	4				
		3.0	5	2	3			5				1	4				

A composite summary of the tests of all these contrast agents in the 70 per cent concentration made with the animals in the supine position is presented in Table 8. Urokon is clearly of a different order of toxicity than any of these agents. At one-quarter and one-sixth the dosage level of the other media that produced minimal to mild changes, severe toxic effects were still encountered with Urokon. Hypaque and Renografin are the least toxic, with Diodrast and Miokon occupying an intermediate position in the order of toxicity.

DISCUSSION

The lack of significant differences between the toxicity of Hypaque and Renografin is not surprising in view of the fact that the only difference in the higher concentration of the two agents lies in the differing proportions of sodium and methylglucamine salts (Table 1). Urokon, or sodium acetrizoate, is quite similar to the basic Hypaque and Renografin molecule—sodium diatrizoate—the only difference being the absence of an additional acetylamino group in the former (Fig. 1). Our studies demonstrate adequately that the addition of the acetylamino group to the acetrizoate molecule reduces strikingly its local toxic effect on the spinal cord. This finding is in complete agreement with the observations of Langecker *et al.*[2] and Moore and others[5] with regard to the general toxicity of these compounds.

The conclusions drawn from this study regarding the relative toxic effects of various contrast media on the spinal cord of the dog are in agreement with previous studies in which the brain was used as the testing site. Workers at Winthrop Laboratories[6] studied the relative toxic effects of Urokon, Hypaque, and Diodrast, using injury to the blood-brain barrier of the rabbit as their principal criterion of a toxic action. Using enormous test doses (25 cc. at a rate of 2 cc. per sec.), they found that the order of increasing toxicity was Hypaque, Diodrast and Urokon. Bloor, Wrenn and Margolis[1] using electroencephalographic changes, barrier disturbances, and early anatomical changes as the criteria of injury, found 30 per cent Urokon to be approximately four times as toxic on the rabbit brain as 35 per cent Diodrast. Whiteleather and DeSaussure[7] compared the toxic effect of 50 per cent Hypaque, 35 per cent Diodrast, and 30 and 50 per cent Urokon on the brain of the dog, using barrier disturbances, respiratory effects, and the immediate convulsive response as indicators of toxicity. Significant reactions or evidence of disturbances of permeability did not occur with 35 per cent Diodrast or 50 per cent Hypaque even when amounts as high as 50 cc. of either agent were given in a single injection. These workers, however, did not compare directly equal concentrations of these two agents. Thirty per cent Urokon caused little respiratory or convulsive response, but did produce definite injury in amounts of 30 cc. in single injections. The injection of 50 per cent Urokon, even in doses of 10 cc., resulted in convulsions and impairment of the blood-brain barrier in various degrees.

In our studies there was an excellent correlation of the three criteria of injury in the severe toxic reactions (Table 8). But, in the lesser grades of

injury this correlation was not so exact, the anatomic lesion being a far better indicator of a toxic effect than the convulsive reaction or the residual neurologic deficit.

SUMMARY

1. A new method which employs the spinal cord of the dog as the testing site and which uses as criteria of injury the immediate convulsive response, the residual neurological deficit, and the resultant anatomic cord lesions has been used to test the toxicity of five contrast media designed for use in arteriography.

2. Of the criteria of injury, the anatomic lesions of the cord proved to be the most sensitive, determinate, and quantitative index of toxicity.

3. The tests showed that Urokon was the most toxic agent tested. Renografin and Hypaque were equal with respect to toxicity and were less toxic than the other media. Diodrast and Miokon were intermediate in toxicity between the other agents and were about equal to each other in this respect.

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LACTIC DEHYDROGENASE OF CEREBROSPINAL FLUID IN THE DIFFERENTIAL DIAGNOSIS OF CEREBROVASCULAR DISEASE AND BRAIN TUMOR

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A SIMPLE, rapid, safe and effective means of distinguishing cerebrovascular disease from expanding intracranial lesions would be of use in those cases in which the history, examination and diagnostic study lead to uncertain conclusions. Apoplectiform symptoms as an early sign of an expanding lesion and the displacement of ventricles by thrombosis of major blood vessels simulating tumor have been confusing to many. The present work indicates that the level of the enzyme, lactic dehydrogenase, in cerebrospinal fluid is elevated in cases of cerebrovascular disease as compared with patients afflicted with intracranial tumors.

Although the utilization of the lactic dehydrogenase level as an index of cerebrovascular disease does not replace clinical judgment it may prove a useful technique in the armamentarium required for the differentiation of these two disease entities. The method is both simple and rapid and thus prompts the present preliminary report.

ASSAY METHOD

Lactic dehydrogenase catalyzes the following reaction:[8]

$$\text{Pyruvate} + \text{DPNH} + \text{H}^+ \rightleftarrows \text{Lactate} + \text{DPN}^+$$

Advantage is taken of the fact that one of the substrates, DPNH* has a high light absorption ($\epsilon = 6.22 \times 10^3$)[3] at a wavelength of 340 mμ whereas the other components of the assay and the products of the reaction do not absorb significantly at this wavelength. The reaction may therefore be conveniently followed in a spectrophotometer by observation of the decrease in optical density at 340 mμ. Under the conditions to be outlined the initial decrease in optical density has been found to be linear with time and directly proportional to the quantity of lactic dehydrogenase.

In practice the following components were added per ml. of reaction mixture: water, 0.55 ml.; M phosphate buffer at pH 7.5, 0.05 ml.; 0.002 M DPNH†, 0.05 ml.; CSF, 0.3 ml.; 0.1 M pyruvate at pH 7.5, 0.05 ml. A blank cell contained only water. Pyruvate was added 3 minutes after the other components and was used to initiate

* DPN and DPNH refer to the oxidized and reduced forms of diphosphopyridine nucleotide, respectively.

† The compound is relatively unstable in solution. It has been found convenient to adjust DPNH solutions to pH 8.0 and, when not in use, to store them in a freezing compartment for no longer than 1 week.

the reaction. After the addition of pyruvate the optical density at 340 mμ was determined at half-minute intervals for 3 minutes and the rate of change per minute was calculated. One unit of lactic dehydrogenase is designated as the amount of enzyme that results in a change in optical density at 340 mμ of 0.001 per minute. Results are recorded in units of activity per 0.3 ml. of CSF and designated by the symbol, μ.

Curve A of Fig. 1 depicts the results of a typical assay. It will be noted that in this case the optical density decreased, i.e. DPNH was oxidized,

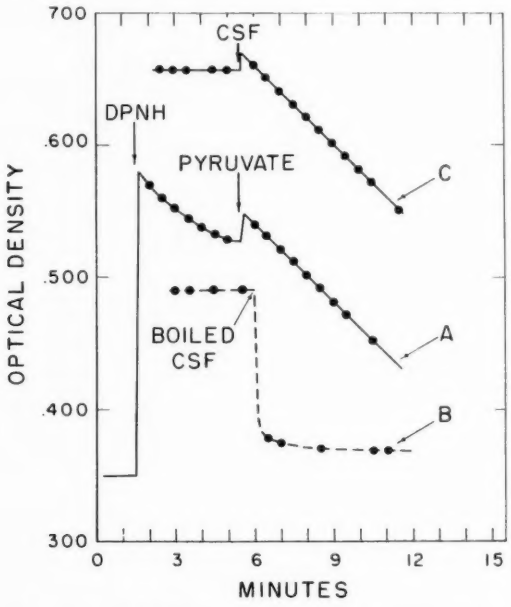

FIG. 1. Assay conditions. Curve A: CSF incubated in buffer. The arrows denote the time of addition. Curve B: Crystalline lactic dehydrogenase of muscle (0.1 mg.) incubated in the presence of buffer and DPNH. A boiled sample of CSF is added at the arrow. Curve C: Pyruvate and DPNH incubated in buffer. The same sample of CSF as is present in Curve A is added at the arrow. Note that the rates in Curves A and C are identical.

without the addition of pyruvate. This reaction is caused by the presence of a substrate for an enzyme already present in cerebrospinal fluid. That this substrate is in fact pyruvate may be shown by the addition of a sample of spinal fluid which had been boiled so as to inactivate the lactic dehydrogenase of cerebrospinal fluid, to a cuvette containing DPNH and crystalline lactic dehydrogenase of muscle (Curve B). Furthermore, the 2,4-dinitrophenylhydrazine derivative of pyruvate isolated from a sample of cerebrospinal fluid had a melting point identical to that of an authentic sample. Assay of 50 samples of cerebrospinal fluid for pyruvic acid by an independent method[1] revealed that the pyruvate content ranged from 0.04 to 1.5 micro-

moles per ml. of cerebrospinal fluid. Although pyruvate levels are elevated in pathological fluid, particularly in meningitis, an accurate correlation between content of pyruvate and pathology can not be made.

Dialysis of cerebrospinal fluid against a solution of 0.05 M potassium phosphate at pH 7.0 and 0.01 M thioethanol for 12 hours removed all endogenous activity. When pyruvate was added the rate of the reaction was within 10 per cent of that of the original undialyzed sample. The rate of DPNH oxidation can be made independent of endogenous substrate by the addition of pyruvate to the reaction mixture (Curve C). Thus, the rate of decrease of optical density at 340 mμ under the conditions outlined here is proportional only to the quantity of lactic dehydrogenase present in spinal fluid.

Samples of cerebrospinal fluid are stable for as long as 2 weeks at 4° C. Although obviously not desirable, samples may be kept at room temperature for several hours. In this study blood-tinged or cloudy samples of cerebrospinal fluid were rejected.

RESULTS

Patients in this series were divided equally with respect to sex and varied in age between 2 months and 81 years. Although no attempt was made to select cases it is inevitable that a certain natural selection is involved. Lumbar puncture is not a routine procedure so that even in those subjects labeled as "non-neurological," suspicion of possible neurological involvement must have existed. With this in mind the data of Fig. 2 will be considered.

Non-neurological. The cases in this group include diagnoses of hysteria (Table 1), pneumonia (2μ, 4μ, 11μ), cardiovascular disease (7μ, 10μ, 11μ), cirrhosis (11μ, 18μ), arthritis (16μ), mastoiditis (2μ), pyelonephritis (4μ), gastric ulcer (3μ) and diabetes (15μ). An average of 10μ was obtained for 20 cases.

Neurological. The results for many of the neurological cases are summarized in Table 1. Also included in this category were cerebral atrophy (13μ, 17μ), pseudotumor cerebri (2μ), aneurism of the internal carotid (10μ) and Friedreich's ataxia (14μ). Among the head injuries is one case of subdural hematoma (8μ) and a skull fracture (20μ; protein 95 mg. per cent).

It is of interest that in 2 cases of complete block resulting from a herniated intervertebral disc, lactic dehydrogenase levels of 7μ and 10μ were obtained although the cerebrospinal fluid protein was assayed as 96 and 114 mg. per cent, respectively.

The average level in 58 neurological cases was 10μ.

Although they have been excluded from statistical calculations, assays have been made in 4 cases of meningitis. Each of these patients yielded lactic dehydrogenase values (32μ, 44μ, 50μ, 65μ) in the range obtained with cerebrovascular accidents.

Tumor. The diagnosis of brain tumor was confirmed at operation or necropsy in 13 of 17 cases. In 4 cases not so confirmed the diagnoses were metastatic lesions and a third ventricle tumor. Included in this series are

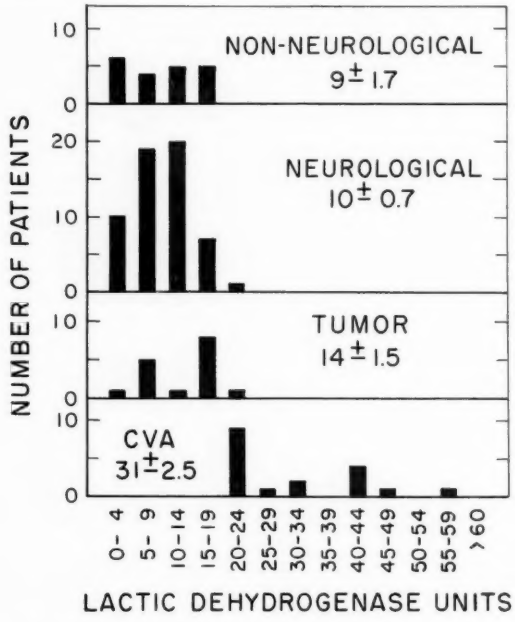

FIG. 2. Distribution of lactic dehydrogenase levels. The average value and the standard error of the mean are given for each series.

meningioma (8μ, 19μ), ependymoma (7μ, 23μ), third ventricle tumor (7μ), bilateral papilloma of the choroid plexus (2μ), pituitary tumor (17μ), astroblastoma (15μ), oligodendroglioma (15μ), astrocytoma (5μ, 19μ), glioblastoma (15μ, 18μ) and brain metastasis (Table 1). It is of interest that the cerebrospinal fluid protein was above the normal limits in most of these cases.

The average for all tumors was 14μ.

TABLE 1

Lactic dehydrogenase in several disease states

Diagnosis	No. of Cases	Lactic Dehydrogenase (μ)	
		Mean	S.E.*
Hysteria	5	10	±2.0
Brain metastasis	4	15	±2.9
Convulsive disorders	14	10	±1.1
Multiple sclerosis	5	9	±2.6
Head injuries	7	12	±2.5
CNS syphylis	3	12	±1.8
Disc syndrome	15	8	±1.3
Meningitis	4	48	±6.9

* Standard error of the mean.

Cerebrovascular Accidents. These cases were diagnosed by a typical history, physical findings and diagnostic tests. No distinction is made here between emboli, thrombosis and hemorrhage. In 12 of 18 cases the diagnosis was verified by postmortem examination. One case of subacute bacterial endocarditis (22μ) with brain emboli found at necropsy is included.

In cases in which more than one sample of cerebrospinal fluid was available, the highest value was recorded. It will be noted that assay values are generally higher when cerebrospinal fluid was obtained several days after the onset of symptoms (Fig. 3). The average value for this series was found to be 31μ.

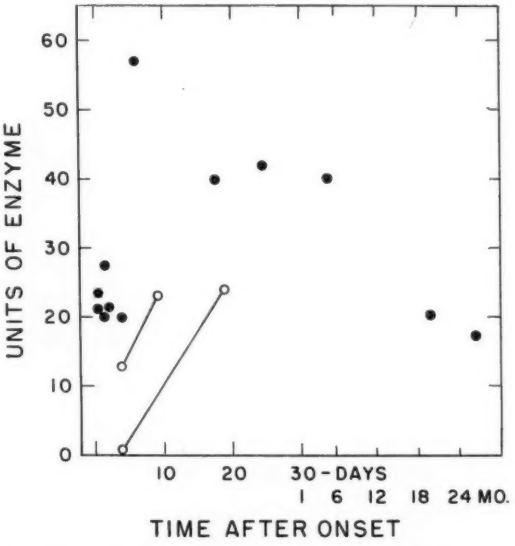

FIG. 3. Lactic dehydrogenase levels as a function of time after appearance of symptoms. Connected points refer to serial lumbar punctures on the same patient.

DISCUSSION

The discovery by Karmen *et al.*[5] that the concentration of transaminases in human serum is elevated following myocardial infarction has led to the use of this valuable tool in the differential diagnosis of that disease.[6,7] The cellular destruction occurring in the anoxic myocardium is thought to release the enzymes into the blood. Similar reasoning has been employed with respect to the formation of anoxic areas in the brain following cerebrovascular accidents. The results presented here clearly substantiate this argument. Comparison of the average value for lactic dehydrogenase in cerebrovascular accidents with that of all other samples of cerebrospinal fluid tested yields a p value of less than 0.001, i.e., the possibility of these differences being ascribable to chance is less than one in a thousand. While the present work

was in progress Green *et al.*[2] have assayed the cerebrospinal fluid of 12 normal patients and 12 patients with cerebrovascular accidents for glutamic-oxalacetic transaminase and have demonstrated elevated transaminase levels in those with cerebrovascular accident.

Lactic dehydrogenase was used in this study because of the simplicity of the assay, i.e., only DPNH and pyruvate are required. Assays of aspartic-α-ketoglutaric transaminase require the addition of malic dehydrogenase and, because of the presence of pyruvate in cerebrospinal fluid, are subject to errors because of the action of glutamic-pyruvic transaminase and, more particularly, of lactic dehydrogenase. The relatively large amounts of pyruvate present in cerebrospinal fluid, i.e., up to 0.0015 M, would not be removed during the preincubation period employed in the usual transaminase assay.[4]

Clearly the usefulness of such assays depends on the ability to distinguish between disease states that may mimic cerebrovascular accident. Cases of cerebrovascular accident in this series fall between values of 20 to 57. Meningitis, a head injury and one tumor also yielded values in this range. Meningitis and injury can be ruled out on other grounds. Tumors, however, may give rise to anoxic brain with results similar to those caused by cerebrovascular accidents. From the data presented it would seem that such events are infrequent and that higher values of lactic dehydrogenase, i.e., above 30μ, weighed with the clinical evidence should be diagnostic for cerebrovascular accident.

It should be noted here that the data presented for cerebrovascular accident are somewhat biased in that only those patients who required hospitalization were available for study and it is conceivable that in cases of "little-strokes" the assay values may be lower.

The pattern of enzyme increase is noteworthy. Lactic dehydrogenase levels may be low soon after symptoms appear and increase only after some days. In this connection it has been found[9] that dogs subjected to cerebral anoxia simulating cerebrovascular accident yield very high levels of transaminase within hours after infarction and that the enzyme disappears from the cerebrospinal fluid within 10 days. Although experimental evidence is not available, it may be questioned whether patients with cerebrovascular accident who are seen clinically react in a manner and at a rate similar to those of the experimental animals. The possibility does exist that the increased levels of lactic dehydrogenase are not caused by leakage from anoxic brain but rather are a function of repair mechanisms.

SUMMARY

The concentration of the enzyme, lactic dehydrogenase, has been examined in spinal fluids from a series of patients with a variety of disorders. Significantly higher enzyme levels have been found in the cerebrospinal fluid of patients with cerebrovascular accidents as compared with normal individuals and patients with neurological disease including brain tumor.

The test is suggested as useful in the differentiation of cerebrovascular accident from other disease with similar clinical picture.

It is a pleasure to acknowledge the interest and cooperation of Dr. James W. Watts and Dr. George A. Kelser in this work.

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MECHANISM AND CONTROL OF CENTRALLY INDUCED CARDIAC IRREGULARITIES DURING HYPOTHERMIA

PART I. CLINICAL OBSERVATIONS

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CENTRAL influences on cardiac rate and rhythm have been investigated in the operating room and laboratory because of their potentially dangerous effects during cerebral vascular surgery under hypothermia. In the course of these clinical and experimental observations, the effects of drugs and low body temperatures on brain-heart pathways and the action of the heart have also been considered.

Our clinical observations (Part I) are based on electrocardiographic findings during 40 intracranial operations of which 20 were done for cerebral vascular lesions: 19 for aneurysms of the circle of Willis and 1 for a parietal lobe angioma. Hypothermia was employed in 15 of these 20 cases. General anesthesia, consisting of intravenous Pentothal sodium and intratracheal oxygen-nitrous oxide, was administered for 37 of the 40 operations and local anesthesia for 3.

Ancillary experimental studies (Part II)[13] were carried out on over 30 cats to test the effects and thresholds of single and combined or conditioning stimuli of central and peripheral origin on cardiac activity. The influence of certain drugs and of lowered body temperatures upon the nervous system and upon the heart was also tested.

It is our hope that correlation of the clinical and experimental data so obtained will clarify some of the basic principles of brain-heart physiology and thus enable us to reduce or prevent cardiac complications of neural origin during surgery.

Historical. There are considerable data to indicate that cardiac activity in man may be altered by central influences. It is well known, for example, that increased intracranial pressure may induce bradycardia, presumably because of pressure on the vagal nuclei. Additional pressure in turn may lead to tachycardia, possibly because of vagal release or central compensatory mechanisms.

Disturbance of brain-stem function, as from hemorrhage or compression, may also lead to bradycardia or tachycardia, depending on the location and extent of the pathological process. Disturbances of hypothalamic function

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or of the visceral cortex[10] may likewise affect the heart, as exemplified by palpitation and tachycardia in diencephalic[9] or temporal lobe[4] epilepsy. It has, moreover, been shown by White [16] that electrical stimulation of the anterior hypothalamus in patients under ether anesthesia may induce bradycardia, but not when midbrain pathways are blocked by a tumor, or when atropine has been given. Mechanical or electrical stimulation of the anterior cingulate cortex[12] or uncus[5] in man may also alter cardiac rate or rhythm, independently of or together with blood pressure and respiratory changes.

While pain has been induced by manipulative stimuli applied to vessels of the circle of Willis in man,[14] we have found that similar stimuli applied to the circle of Willis may induce alterations in cardiac rate or rhythm, particularly under abnormal conditions imposed by hypothermia, together with insufficient neural blocking.[11]

It is our purpose therefore to present examples of this and related phenomena to illustrate how certain central stimuli may at times alter the rate, rhythm or configuration of the electrocardiogram.

METHODS OF PRESENT STUDY

(a) *Anesthesia.* Approximately 1 hour before induction of anesthesia, each patient was given Demerol 100 mg. (h) and scopalamine 0.4 mg. (h). Immediately prior to craniotomy, moreover, the site of the scalp incision was infiltrated locally with 1 per cent procaine or Novocain in all 40 cases.

The 3 patients operated upon under local anesthesia alone were given additional Demerol by vein from time to time throughout the procedure to render them drowsy but not incapable of response. In one a posterior rhizotomy for tic douloureux was performed; in another, a subtotal temporal lobectomy for psychomotor epilepsy, while in the third no anesthesia other than local Novocain was given until exposure of a bleeding aneurysm of the internal carotid artery was completed.

All other patients were anesthetized with general anesthesia consisting of intravenous drip of Pentothal sodium supplemented by intratracheal administration of oxygen-nitrous oxide.

In all hypothermic cases cooling was induced by placing the patient on a Therm-O-Rite* mattress and then packing the body with ice cubes. Body temperature was constantly recorded by an intragastric electrically recording thermometer.† To some of these patients chlorpromazine was given in 10 mg. amounts to a total of 40 to 110 mg., while succinylcholine was administered to a few others. There was no apparent correlation between the dosage of these drugs and the reported cardiac effects.

(b) *Electrocardiography.* Constant monitoring of cardiac activity was carried out in all hypothermic patients with a cardiotachiscope,‡ and in all but the first 3 hypothermic patients a recording electrocardiographic apparatus was also used, as for all other operations of this series. "Minor" elec-

* Therm-O-Rite Products Corporation, Buffalo, N.Y.

† Tele-Thermometer, Yellow Springs Co., Yellow Springs, Ohio.

‡ Instrument Laboratories, New York.

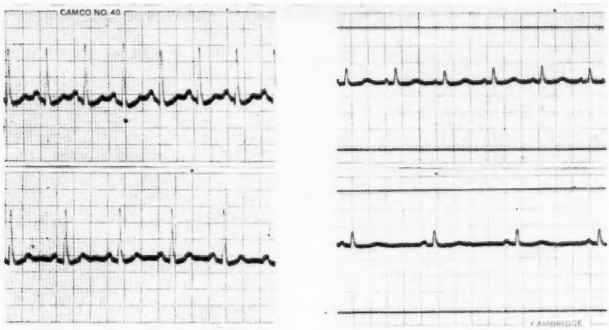

FIG. 1. Bradycardia on subfrontal and hypothalamic retraction. Normothermia. General anesthesia. (*Upper left*) Preceding and (*lower left*) during brief subfrontal retraction. (H.K. prior to direct pallidotomy.) (*Upper right*) Prior to and (*lower right*) during hypothalamic retraction. (N.D. hypophysectomy.)

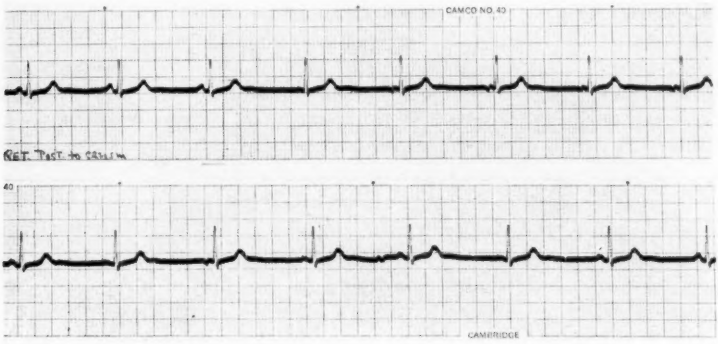

FIG. 2. P wave alteration on hypothalamic and carotid artery manipulation. Normothermia. General anesthesia.

(*Upper record*) P wave inversion on hypothalamic retraction. (*Lower record*) Wandering pacemaker indicated by differing P waves for five beats during brief traction on internal carotid artery. (S.F. hypophysectomy.)

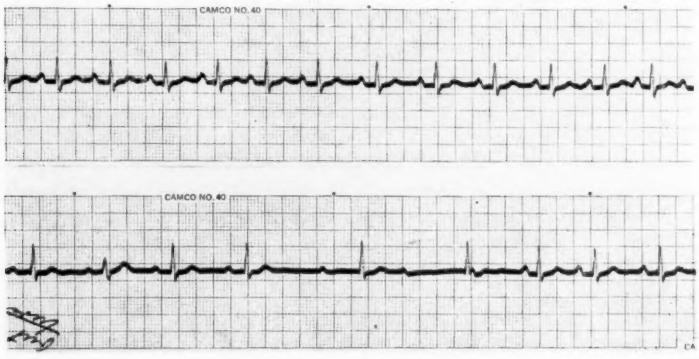

FIG. 3. (*Upper record*) Immediately before hypothalamic retraction. (*Lower strip*) Varying P-R interval and transitory 2:1 block on brief anterior hypothalamic retraction. Normothermia. General anesthesia. (E.S. hypophysectomy.)

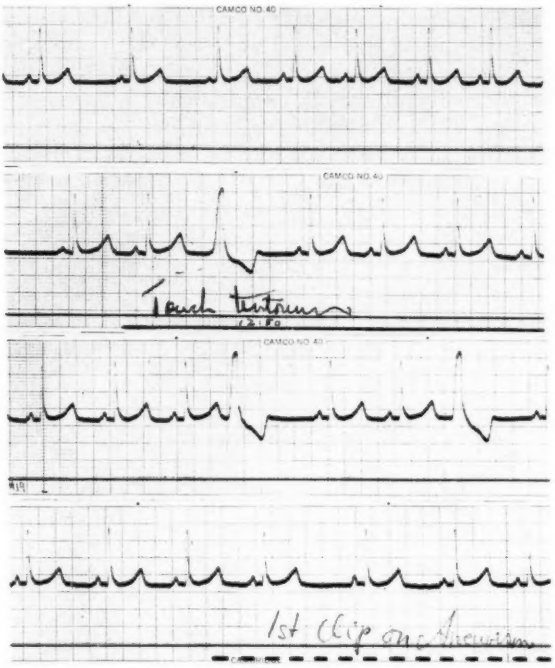

FIG. 4. Ligation of carotid aneurysm. Hypothermia (29.2°C.) and initially light anesthesia. (Case M.W.)

(*1st strip*) Slightly irregular rate characteristic of electrocardiogram during this operation. (*2nd strip*) Tentorial displacement resulting in premature ventricular beat. (*3rd strip*) Dissection of aneurysm resulting in premature ventricular beats. (*4th strip*) 3 min. after 90 mg. Pentothal sodium i.v. Further dissection including clipping of aneurysm (dotted line) now resulting in only slight transitory bradycardia.

trocardiographic changes refer to acceleration or slowing for a few beats, a single P wave alteration, or a premature ventricular contraction. "Major" changes mean prolonged, marked alterations in rate, rhythm or configuration.

(c) *Blood pressure.* A Lilly capacitometer* was used for direct arterial recording of blood pressure in 3 patients, 2 under hypothermia. A standard cuff manometer was used at approximately 1-minute intervals in all other cases.

(d) *Respiration.* The Jefferson automatic respirator† was used for most of the hypothermic and some of the other cases, every effort being made to prevent metabolic acidosis by maintaining adequate ventilation at all times. The CO_2 analyses of the blood made in a number of our more recent hypothermic cases will be reported separately by Dr. Duncan Holaday of the Service of Anesthesiology.

(e) *Plane of Anesthesia.* The depth of anesthesia was deemed "light"

* Lilly Capacitometer, Model 115A1, Technitrol, 3212 Market St., Philadelphia, Pa.

† Air Shields, Inc., Model GH, Hatboro, Pa.

when any manifestations of shivering or slight spontaneous movements occurred or when movements resulted from ordinarily painful stimuli. These effects were judged by inspection of the patient, the electrocardiographic tracings and in some cases by electroencephalographic recordings. When no such manifestations of shivering, movements, etc., were noted, the level of anesthesia was considered to be appropriately "deep."

(f) *Stimuli.* The various manoeuvres during surgery that have been referred to as "stimuli" include postural shifts, dissection of the carotid arteries in the neck, the usual steps in performing a craniotomy such as periosteal stripping, opening of the dura mater, cauterization of the middle meningeal artery, compressing, cutting or cauterizing part of the tentorium, retracting the brain (Figs. 1, 2, 3), or applying gentle traction or pressure on cranial nerves or arteries of the circle of Willis as required for their dissection (Figs. 2, 4, 5, 6).

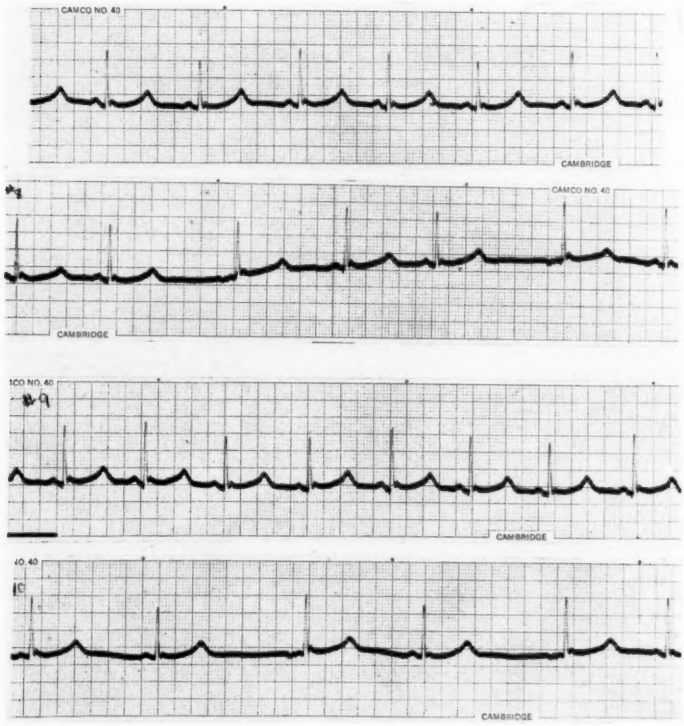

FIG. 5. Dissection of internal carotid aneurysm under general anesthesia and hypothermia (27.1°C.). (Case F.M.)

(*1st strip*) Prior to dissection of aneurysm. (*2nd strip*) During dissection, showing irregular rhythm, slower rate and occasional extra P waves. (*3rd strip*) 4 min. after 90 mg. Pentothal sodium i.v., when EKG showed now no changes in rate or rhythm during or immediately after dissection of aneurysm. (*4th strip*) 15 min. later. Dissection of aneurysm again results in bradycardia, irregularity of rate, and P wave changes suggesting a wandering pacemaker. Light carotid artery traction also resulted in this effect.

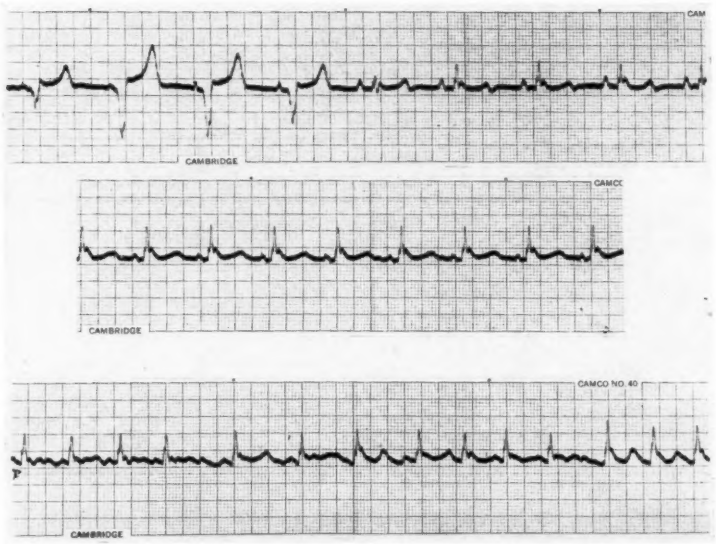

FIG. 6. Bleeding aneurysm of internal carotid artery. Craniotomy begun under local anesthesia only and hypothermia (28.4°C.). (Case E.K.)

(*1st strip*) Spontaneous irregularity of ventricular conduction of several minutes' duration (at left) ceased 30 sec. after 200 mg. Pentothal sodium i.v. (*2nd strip*) 5 min. later. Dissection of aneurysm resulted in no EKG changes. (*3rd strip*) 4 min. later. Auricular fibrillation on further dissection of aneurysm (soon thereafter controlled by additional Pentothal sodium).

It may be emphasized at this point that the marked electrocardiographic changes induced by gently touching or mobilizing aneurysmal sacs were not caused by accompanying retraction of the brain, for such retraction was already being maintained by steady, constant retraction prior to these changes. Nor did tentorial stimulation seem a factor, as control tests by pressing on, cutting or cauterizing the tentorium only occasionally induced minor cardiac changes. Moreover, the reported electrocardiographic changes occurred in several cases when the aneurysmal sac was not adherent to or in continuity with the tentorium. As a rule, furthermore, the reported cardiac changes were not associated with accompanying alterations in the blood pressure.

RESULTS

Of the 40 patients studied 15 were operated upon under hypothermia and 25 at normal body temperature.

Of the 15 hypothermic patients a relatively light plane of anesthesia (see above) of varying duration was purposely or sometimes inadvertently maintained, for varying periods, in 11. In the presence of such light anesthesia major electrocardiographic irregularities (see Electrocardiography) occurred in 9 of these 11 cases, minor changes in 1, and no significant electrocardiographic changes in another. In the 4 remaining hypothermic patients who were deeply anesthetized throughout, no unusual electrocardiographic changes occurred in 3, and only minor changes in the fourth.

TABLE 1

Cases tested

Diagnosis	Normothermic (25)		Hypothermic (15)	
	General Anesthesia	Local Anesthesia	General Anesthesia	Local Anesthesia
Aneurysm	5		13	1
Angioma (parietal)			1	
Parkinson's disease	1			
Dystonia	1			
Pituitary tumor	6			
Craniopharygioma	1			
Meningioma (subfrontal)	2			
Acoustic neurinoma	4			
Trigeminal neuralgia	3	1		
Psychomotor epilepsy		1		
	23	2	14	1

TABLE 2

Manoeuvres and stimuli resulting in electrocardiographic changes

Procedure	Normothermic (25)		Hypothermic (15)	
	General Anesthesia	Local Anesthesia	General Anesthesia	Local Anesthesia
	23 Cases	2 Cases	14 Cases	1 Case
Postural shift	0 (8)*	0 (1)	3 (14) ++	0 (1)
Dissection of:				
Cervical carotid	0 (5)	—	3 (14) ++	0 (1)
Periosteum	0 (23)	0 (2)	2 (14) +	1 +
Dura mater	1 (23) +	1 (2) +	3 (14) +	1 +
Middle meningeal artery	1 (19) +	1 (2) +	3 (14) +	1 +
Tentorium	2 (11) +	1 (2) +	4 (13) +	1 +
Cortical vessels	0 (4)	0 (1)	0 (14)†	0 (1)
Circle of Willis	3 (9) +	1 (1) +	7 (13) ++	1 ++
Aneurysm	1 (5) +	—	7 (13) ++	1 ++
Cranial nerves:				
2, 3, 4, 6	0	0	0	0 (1)
5	1 (3) +	0 (1) ++	—	—
7, 11	0 (4)	—	—	—
9, 10	3 (4) ++	—	—	—
Retraction of:				
Frontal or temporal lobe	13 (19) +	1		1
Hypothalamus	5 (6) ++	—	—	—
Brain stem	1 (1) +	—	—	—

* Numerals in parenthesis indicate number of cases so tested. Open numerals indicate number of patients having electrocardiographic changes from procedure listed.

† Parietal angioma included in this figure.

Plus signs indicate degree of electrocardiographic changes. + = minor; ++ = major (see "Methods").

Of 25 patients at normal temperature under local, light or adequately deep general anesthesia, 15 showed occasional minor electrocardiographic abnormalities, mostly as the result of brain retraction.

Nine patients in this group showed major changes as a result of two types of surgical manoeuvres; that is, anterior hypothalamic retraction (in 5 out of 6 cases) and 9th and 10th cranial nerve compression (in 3 out of 4 cases). In the ninth case cardiac irregularities were present throughout surgery, although the pre- and postoperative electrocardiographic tracings were normal. In this patient, operated on for tic douloureux under local anesthesia, compression of the Gasserian ganglion temporarily restored the electrocardiographic pattern to normal.

In 7 of 11 hypothermic patients with spontaneous or induced electrocardiographic irregularities, the administration of *additional* intravenous Pentothal sodium promptly restored a normal cardiac rate and rhythm and for varying periods prevented recurrence of electrocardiographic abnormalities (Table 3). In the remaining 4 of these 11 patients in whom abnormal electrocardiographic patterns persisted or kept recurring, no additional Pentothal was given to 2; only 30 mg. to another, while in the fourth case with occasional minor electrocardiographic abnormalities, only 30 mg. were given at 20–30 minute intervals.

The case material (Table 1) and the various stimuli or procedures giving rise to cardiac responses (Tables 2 and 3) indicate that minimal or no elec-

TABLE 3

Hypothermia

Case	Anesthesia Plane		Reversion to Normal EKG After Additional Pentothal	EKG Changes		
	Deep	Light		None	Minor	Major
1. F.O.		+				+
2. T.H.		+				+
3. E.W.		+				+
4. N.M.		+	+			+
5. C.M.		+	+			+
6. L.S.		+	+			+
7. M.W.		+	+			+
8. F.M.		+	+			+
9. E.K.		+	+			+
10. P.A. (Angioma)		+	+		+	
11. B.T.		+		+		
12. C.L.	+				+	
13. I.B.	+			+		
14. R.T.	+			+		
15. J.C.	+			+		
	—	—	—	—	—	—
	4	11	7	4	2	9

Average temperature range 27.2°C.–29.2°C.
Average blood pressure range 90/70–80/60.

trocardiographic changes occurred during most of the surgical manoeuvres customarily used during craniotomy under general anesthesia at normal body temperature. For example, in only 3 of 9 cases in this group so tested did light pinching or traction applied to the internal carotid artery at the base of the brain give rise to brief, minor electrocardiographic changes.

Bradycardia, however, was repeatedly noted upon hypothalamic retraction (Fig. 1, right) in 5 of the 6 patients undergoing pituitary surgery, and to a lesser degree in these and other cases, upon retraction of subfrontal (Fig. 1, left), temporal or anterior cingulate cortex. None of the cranial nerves tested (2nd, 3rd, 4th, 6th, 7th, 11th) gave rise to electrocardiographic changes except for bradycardia on gentle compression of the 9th and 10th nerves and, more rarely, the 5th.

Under local anesthesia traction on the circle of Willis, middle meningeal artery, dura mater and tentorium only occasionally elicited minor changes in the cardiac rate, either in the direction of slowing or acceleration, for 3 to 5 beats.

Finally there were no instances of cardiac arrest in these 40 cases. All normothermic patients made an uneventful postoperative recovery and in the hypothermic group there were no failures in recovery caused by cardiac complications.

DISCUSSION

It is well established that changes in the rate or rhythm of the human heart may occur as the result of certain toxic, metabolic or neural stimuli,[1,3,6] from the effects of hypothermia,[2,7,8,15] and from stimulation of certain parts of the brain such as the visceral cortex[10] or hypothalamus.[16]

Our data tend to substantiate these observations with respect to brain stimuli and also with respect to various cranial and intracranial structures such as the periosteum, dura mater, tentorium, the 5th, 9th and 10th cranial nerves, and arteries of the circle of Willis (Figs. 2, 4, 5 and 6).

In some *but not all cases*, as indicated, stimulation of any or all of these structures may be capable of nonspecific effects on the rate or rhythm of the heart. Other factors in addition to the actual stimulation of these structures must therefore have influenced the cardiac response to such stimuli. Of these factors, increased susceptibility or lowered threshold to excitation of both the central nervous system and of the heart appear to be of the greatest importance, as both may be significantly altered either by hypothermia or the level of anesthesia.

That the threshold of neural circuits transmitting impulses to the heart or the susceptibility of the heart to excitation, or both, may be altered by hypothermia, is indicated by our repeated observations that cardiac irregularities induced by cranial stimuli occur most frequently during lowered body temperatures. In 9 out of 15, or 60 per cent, of our hypothermic patients, for example, major electrocardiographic irregularities occurred, and minor electrocardiographic changes in 2 others. When compared to the infrequency of *major* electrocardiographic abnormalities during normothermia,

the lowered threshold of excitability of the heart and/or its central nervous connections by hypothermia seems obvious. Since standard techniques were used in all of the intracranial operations mentioned, moreover, it can be safely assumed that stimuli in all these cases were relatively similar and comparable, and that whereas minor cardiac changes were predominant in normothermic patients, far greater cardiac effects were generally induced by similar cranial stimuli in hypothermic patients.

Another indication that threshold may be an important factor in influencing cardiac irregularities of central origin is the relationship of the plane or depth of anesthesia to the frequency of cardiac changes. Of our 11 hypothermic patients who were *lightly anesthetized*, for example, 9 exhibited major, while only 1 exhibited minor and 1 no significant electrocardiographic abnormalities during surgery. Of 4 *deeply anesthetized* patients in this group, however, only 1 showed minor electrocardiographic changes and 3 none. While in the normothermic patients we could make no correlations between the plane of anesthesia and electrocardiographic changes, in the hypothermic cases it clearly appeared that alteration of central nervous thresholds by anesthesia was an important variable that could influence the occurrence of cardiac irregularities during intracranial surgery.

This principle is further illustrated by 7 of 11 hypothermic patients (Table 3) in whom cardiac abnormalities promptly disappeared after the intravenous administration of additional Pentothal sodium, as illustrated in Figs. 4, 5, and 6. Of the 4 remaining patients in whom an abnormal electrocardiographic pattern persisted, no additional Pentothal was given after the induction of anesthesia in 2. In a third patient, who received only 30 mg. of Pentothal, auricular fibrillation began with the onset of surgery and did not revert to a normal pattern until closure of the wound when brain and cranial manipulation had ceased, although the degree of hypothermia remained essentially unchanged throughout. In the fourth patient, to whom only small, repeated doses of Pentothal were given, minor electrocardiographic changes were frequently recorded during the operation.

It therefore appears that during intracranial surgery hypothermia tends to increase the number and severity of cardiac abnormalities in lightly anesthetized patients, while in hypothermic patients who are more deeply anesthetized the frequency and severity of cardiac abnormality is appreciably less. In lightly anesthetized, hypothermic patients, moreover, cardiac arrhythmias may be corrected or prevented by additional Pentothal sodium. We feel therefore that it is propitious to provide an adequate depth of anesthesia when hypothermia is used for intracranial surgery in order to counteract the increased sensitivity of the heart and its central nervous system connections occasioned by hypothermia.

Finally, it may be emphasized that manipulation of vessels of the circle of Willis may give rise to electrocardiographic changes[11] which are also influenced by the level of anesthesia and body temperature.* While the

* Thanks are expressed to Dr. Lester A. Mount and Dr. Joseph Ransohoff for permission to include their cases illustrating these phenomena.

mechanism of this effect is not yet understood, hypothalamic and/or brain-stem pathways concerned with cardiac regulation are probably disturbed either as the result of temporary vascular or neurogenic reflex changes originating from manipulation of the basal cerebral arteries. That is, these and other central stimuli apparently affect the heart by altering the activity of the neuraxis and thence the heart via the vagal or sympathetic outflow (Fig. 7). Retraction of the brain or hypothalamus presumably exerts a direct

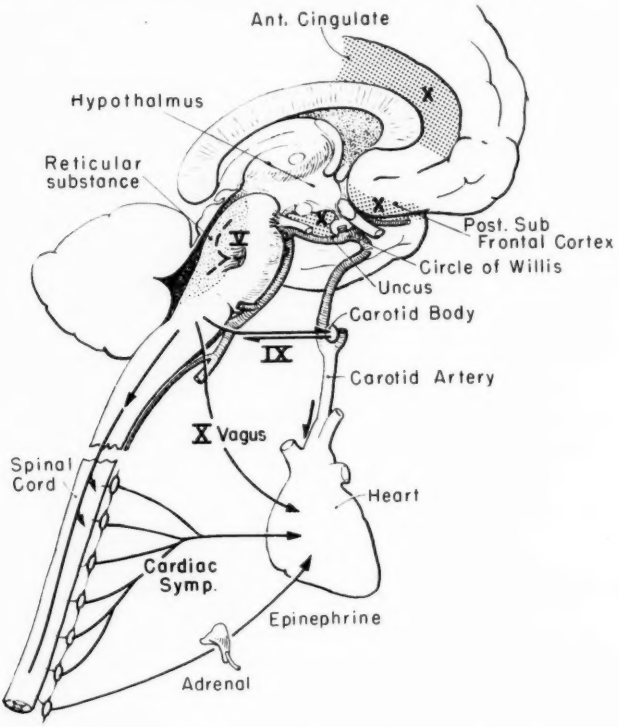

FIG. 7. Diagram of cerebro-cardiac connections referred to in text.

effect on cerebro-cardiac pathways, as does vagal and glossopharyngeal nerve stimulation. Stimuli applied to extra-axial structures such as the periosteum, dura mater, tentorium and vessels of the circle of Willis are somewhat less direct in their effects in the sense that these structures are all innervated by branches of the trigeminal nerve, stimulation of which presumably activates brain-stem relays ultimately capable of influencing cardiac action, similar to the mechanism of the oculo-cardiac reflex. In line with this thought is one case of trigeminal neuralgia in which existing cardiac irregularities during surgery could be stopped by pressure upon the Gasserian ganglion.

With regard to electrocardiographic changes resulting from stimulation of the circle of Willis, still another possibility must be considered; namely, that manipulation may result in local vascular reflex spasm capable of altering the circulation and thus the function of the hypothalamus. From all our clinical and laboratory observations, however, it does not appear that stimuli applied to the circle of Willis affect the electrocardiogram via the descending perivascular autonomic nerve supply.

SUMMARY

1. Electrocardiographic studies were carried out on 40 patients during intracranial surgery. Hypothermia was used in 15.

2. Alterations in cardiac rate or rhythm were uncommon at normal body temperature, but occurred frequently when hypothermia was used together with a light plane of anesthesia. Additional Pentothal sodium not only restored a more nearly normal rate or rhythm but tended to prevent electrocardiographic abnormalities.

3. A variety of central as well as peripheral stimuli were capable of affecting the cardiac rate or rhythm in susceptible patients. Of these, the most common central stimuli were retraction of the frontal or temporal lobes or hypothalamus, gentle compression of the 9th and 10th cranial nerves, and traction upon vessels of the circle of Willis.

4. It is suggested that hypothermia may not only render the heart but also central synaptic relays more susceptible to imposed stimuli unless protection is afforded by adequate blocking agents.

5. Mechanisms are discussed by which the electrocardiogram may be affected by mechanical stimuli applied to vessels of the circle of Willis.

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THE PATHOLOGY OF SUPRATENTORIAL ANGIOMAS*

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THE origin and anatomy of the cerebral angiomas has frustrated pathologists over the years as much as their treatment has baffled surgeons. An extensive literature has developed, replete with picturesque nomenclature based upon attempts to describe the appearance of lesions seen at the operating table or at necropsy. It is believed that no useful purpose would be served now in reviewing these and attempting to explain them in light of present information. The surgical descriptions are not entirely basic nor accurate because the bulk of the lesion is largely submerged under the cortex and hence invisible to the examiner. The pathologic descriptions have been faulty because of deflation of the lesions at the time of examination by lack of the expansile blood stream that characterizes them in life. Also confusing the picture of the dead lesion are the alterations produced in the component vessels by blood under arterial pressure, which dilates veins and "arterializes" them to withstand the added stress. Vascular resistance being lowered by the shunt, arteries dilate to carry more blood under less than usual pressure, and lose some of their usual characteristics. Histologically the lesions appear only as a tremendously convoluted mass of arteries, veins and intermediate types of vessels of extremely variable diameters traversing cerebral tissues altered in structure by the intervening and now deflated vessels.

CLASSIFICATION

Cushing and Bailey[2] were able to separate the "intracranial blood-vessel tumors" into two principal groups, a) the hemangioblastomas, truly neoplastic masses confined chiefly to the posterior fossa, and b) the largely supratentorial group composed of blood vessels contained within cerebral tissue. We are concerned with the latter group. Cushing and Bailey divided these into a) telangiectases, b) venous angiomas and c) arterial (arteriovenous) angiomas. Again, it is with the latter two groups that we are concerned. Olivecrona and Riives[9] agreed with Cushing and Bailey that these are histologically inseparable; the difference is physiologic and depends upon the degree of arterialization of the lesion. Upon the advent of angiography it became apparent that earlier expressed suspicions against the existence of purely venous angiomas were well grounded; in all reported cases the

* Presented at the First International Congress of Neurosurgery, Brussels, Belgium, July 21–28, 1957.

lesions have proved to have arterial supply. The last persisting possibility remained in the very small intracerebral clusters of veins that occasionally are seen largely destroyed in the walls of intracerebral hematomas. Dorothy Russell[12] was able to find a little better than usually preserved example of this type and histologic examination showed it to contain vessels having elastic laminas characteristic of arteries. It seems that there is little if any pathologic evidence to support the concept of purely venous angiomas. Physiologically there is reason to question why a cluster of veins deep within the cerebrum should rupture and produce a massive clot. It is believed reasonable then to ignore these time-honored concepts and to concentrate upon the pathology of the common arteriovenous malformation.

GROSS APPEARANCE

The malformation usually is cone-shaped, its base being on the surface and its apex near or intruding into a lateral ventricle. The apex may be demonstrated at times in cerebral air studies as a projection into the ventricle, and this may be lobulated, because of dilated veins on its tip. In most lesions large enough to produce symptoms leading to their disclosure, dilated cortical veins drain from the lesion and run to one or more of the dural venous sinuses. It is the appearance at operation of these huge veins, often bright with arterial blood, that has fathered so many of the colorfully descriptive titles given the lesions. Since the use of angiography, it has become recognized that many of them, especially behind the fissure of Rolando, also drain into the deep cerebral veins and thence into the Galenic system.[10,14] Some, of course, drain exclusively by this route.[1,6]

The arteries supplying the lesion usually are inconspicuous in the gross specimen, the large parent trunks being buried in the cerebral fissures and their branches being smaller than the more superficial dilated veins. The parent arterial trunk is usually that of the lobe of the brain harboring the mass, and commonly this means more than one vessel. The importance of supply from the posterior cerebral artery and the choroidal arteries has become properly appreciated only since the employment of angiography in diagnosis.

Inspection of the dead lesion shows it to be a spongy mass intruding into the brain substance. When it is cut across, the area containing the draining veins may appear cavernous. The complex of large veins usually lies within the subarachnoid spaces, which are expanded by the mass of vessels. Below this, and extending through the vascular cone of the lesion, the white matter is laced with numerous channels of various diameters. The identity of these vessels is impossible grossly, and very difficult under the microscope. Angiography provides an admirable method of delineating the gross vascular structure of the lesion and Potter[11] considered this the most reliable facility at our command for the study. Unfortunately, it does not sharply reveal the vessels that usually intervene between the arterial and venous sides of the circulation. It was believed that dissection of such a lesion under the microscope might add information. Simmonds[13] illustrated his Case 2 in this

manner. The only recent report found of such a dissection was that by Padget,[10] of a complicated midline lesion supplied by branches of the posterior cerebral arteries, draining into the vein of Galen. Another, perhaps better method of investigation would be to inject a freshly irrigated lesion with acrylic or liquid latex through its supplying arteries and to remove the organic matter by digestion. Unfortunately, specimens favorable for such preparations are difficult to find. Apparently even fixed ones no longer exist

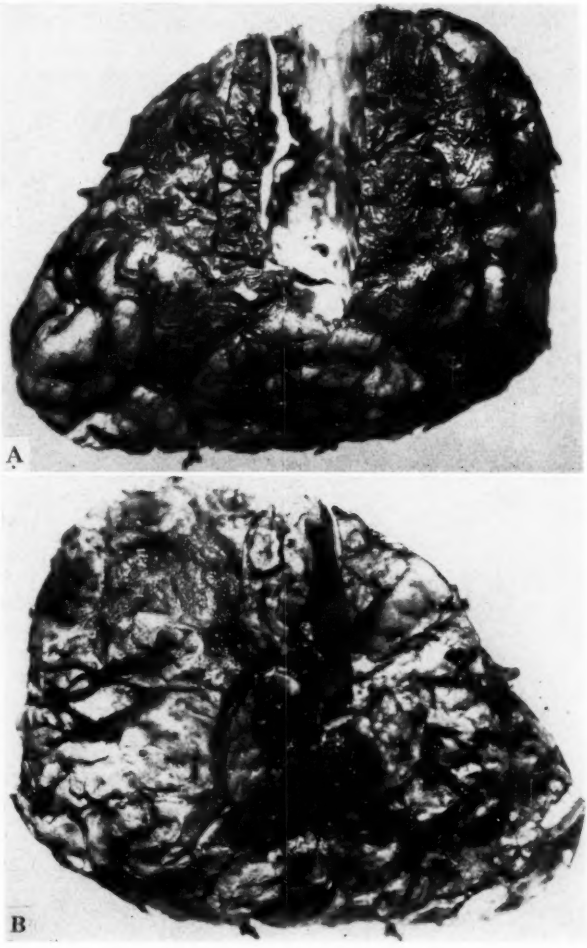

FIG. 1. (A) Lateral view of surgically removed right occipitoparietotemporal lobe. A section of the central portion of the arteriovenous malformation has been excised for histologic study. The draining veins are especially prominent. (B) Mesial surface of the specimen. Large veins destined for the vein of Galen are seen anteriorly, and a surface plexus of smaller vessels is present below the defect produced by removal of specimen for microscopic study.

in many museums of pathology, at least in the United States. As did Cushing and Bailey in preparing their monograph, it was necessary to solicit from friends to find a specimen for this study.

This specimen consisted of a right parieto-occipital lobe (Fig. 1) containing a complicated malformation fed by the right middle and anterior cerebral arteries (Fig. 2) and draining into both the Rolandic and Galenic venous systems. Unfortunately this specimen had been so sectioned that its major supplying vessels were not identifiable. Angiography indicated that they entered the sides of the lesion. When the pia-arachnoid with its complex

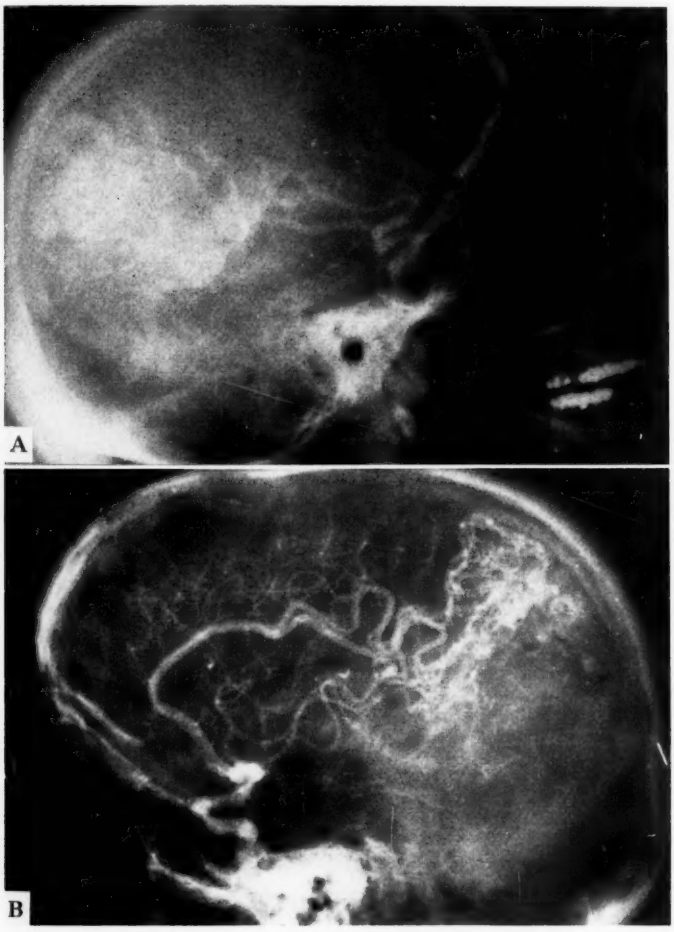

FIG. 2. (A) Right carotid angiogram showing dilated middle cerebral branches entering the mass. Note venous drainage by both Rolandic and Galenic veins. (B) Left carotid angiogram showing greatly dilated *right* anterior cerebral artery entering the malformation.

vascular connections was dissected from the brain tissue and floated in water, the vascular core of the lesion was well indicated by the white central area, containing wide transected veins on its surface. The vessels converging upon it are seen in contrast through the transparent pia-arachnoid. In Fig. 3, a photograph of the partly dissected central core, are seen long, relatively straight vessels containing clotted blood, running toward the apex, dividing into a complex of coiling, intercommunicating vessels that emptied finally into thin-walled tortuous veins. These were continuous with those at the periphery of the central cone of the pia-arachnoid portion of the lesion.

Along the sides of the mass, vessels with walls relatively thick in relation to the lumen formed a rather compact plexus of richly communicating tough-walled, transparent, empty vessels between which the white matter was sparse and fibrous (a, Fig. 4).

Between the surface and Galenic poles of the lesion was an intermediate zone in which the ratio of white matter to vessels was greater. The white matter was loosely arranged parallel to the vessels and, in the collapsed state of the specimen, formed loose, wide perivascular spaces. Approximately four types of small vessels were distinguishable here. The first (1, Fig. 4) resembled those of the earlier mentioned plexus, being empty and relatively firm with uniform lumens measuring from 0.15 to 0.5 mm. in diameter. These were coiled spirally and oriented longitudinally, intercommunicating infrequently.

The second type of vessel (2, Fig. 4) was a thin, relatively infrequently

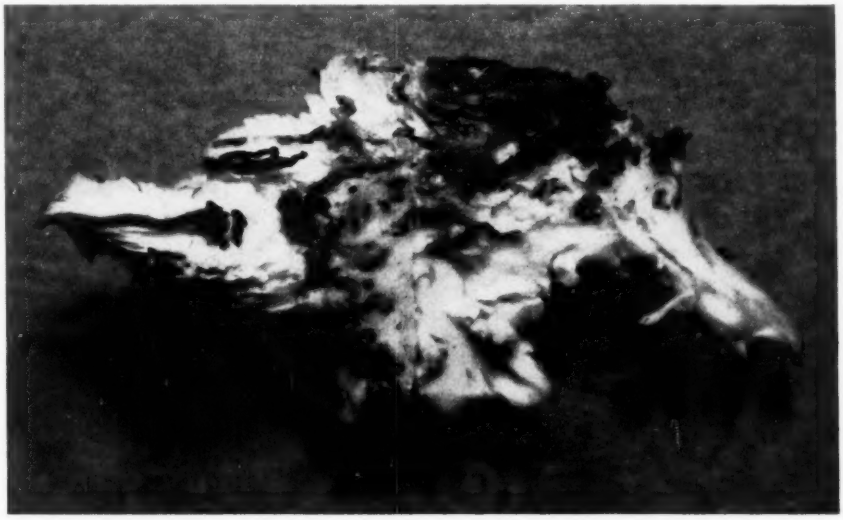

FIG. 3. Photograph of cerebral core, partly dissected. Quite straight, sparsely branching vessels, 2-3 mm. in diameter, run inward to join a zone of smaller complexly coiled and branching vessels which enter wide, thin-walled veins at the top of the specimen. These connected with the periphery of the pia-arachnoid vascular cone shown in Fig. 4.

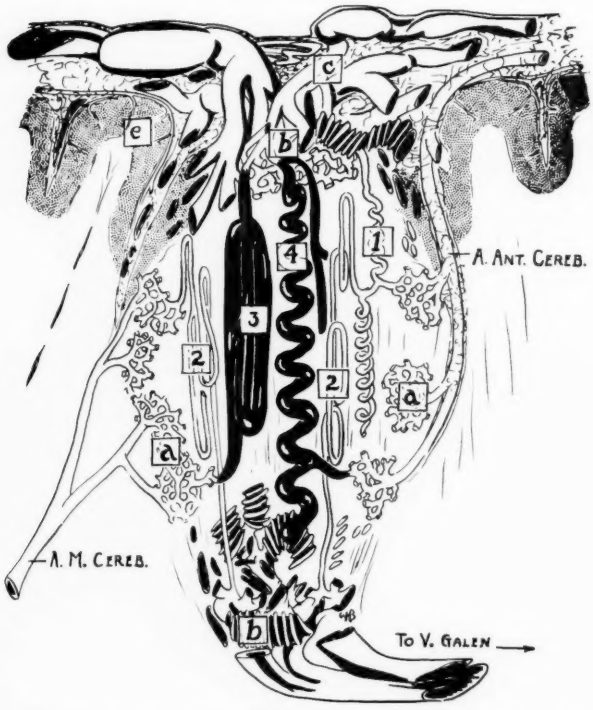

Fig. 4. Schematic drawing of vessels comprising an arteriovenous malformation. (a) Plexus of small, transparent, richly intercommunicating vessels apparently interposed between arterioles and veins (Fig. 5); (b) zone of venous collection (d, Fig. 5); (1) coiled spiral of thin, empty, transparent, narrow vessels (a, Fig. 5); (2) similar type of vessel, coiled longitudinally; (3) wider, longitudinally coiled vessels filled with clot; and (4) similar, but spirally coiled vessel.

branching and intercommunicating tube 0.3–0.5 mm. in diameter. They were straighter, but often looped sharply and formed long, loose coils oriented longitudinally to the axis of the vascular cone.

Vessels of the third type (3, Fig. 4) contained clotted blood. They were wider, 0.4–0.7 mm. in diameter, and when dissected from white matter, resembled earthworms. These also were relatively straight, and arranged in loose coils oriented to the long axis of the vascular cone.

Vessels of the fourth type (4, Fig. 4) resembled the latter except that they were extremely tortuous and convoluted, coiling transversely to the axis of the malformation. They were from 0.3–1.0 mm. in diameter, and were filled with thrombi. They were so wide in relation to the thickness of their walls that they broke very easily despite the gentlest removal of surrounding white matter. It was noticed that in this surgical specimen, it was among the convolutions of these vessels that the majority of small traumatic hemorrhages had occurred.

At each end of the malformation (b, Fig. 4) these vessels entered very thin-walled channels of relatively tremendous diameter (1–5 mm.). In their collapsed state they were flattened into accordion-like pleats. More superficially these connected with progressively wider and more infrequently placed vessels grossly resembling large veins (c, Fig. 4). It was not determined whether all four types of vessels entered the draining veins individually, or whether they gradually coalesced as they approached this zone. In some instances they were seen to communicate directly; in others their identity became lost in a confusion of layers of loose, collapsed vessel walls. In this outer zone (c, Fig. 4) the white matter became gradually less prominent and finally disappeared as the subarachnoid space was approached. The vessels on the surface were covered and surrounded by typical strands of the pia-

FIG. 5. Vessels disclosed by microscopic dissection. (A) Chiefly type 2 (Fig. 4) vessels, with a type 1 vessel at X. (B) Chiefly type 4 vessels. (C) Connection of several type 3 vessels. (D) Junction of small connecting vessels with a large vein-like one (opened, under dimension marker).

arachnoid. Over the center of the lesion this formed a relatively dense feltwork of tissue with small tissue spaces. Toward the periphery the proportions gradually reverted to those of the normal subarachnoid space.

The surface veins in the pia-arachnoid were tremendously dilated and tortuous. This was true not only of those extending to the dural sinuses, but evidences of the venous back-pressure was apparent in the tortuous dilatation of veins covering the entire surface of the otherwise normal cerebral lobe (Fig. 1).

HISTOLOGY

The histologic appearance of arteriovenous malformations has been adequately described by various authors, especially by Cushing and Bailey. Sections through the cerebral portion of the mass show a complex of variously cut blood vessels contained within altered cerebral tissue. The vessels themselves are difficult to identify accurately (Fig. 6). Arteries and arterioles thin and dilate, losing much of the internal elastic lamina, probably as the result of lowered intravascular pressure. Veins dilate and their walls thicken to withstand abnormal pressure. Between the two are small, unidentifiable types of vessel, some composed of little more than intima supported by collagen and condensed glial fibers. Some have walls like glass tubes, re-

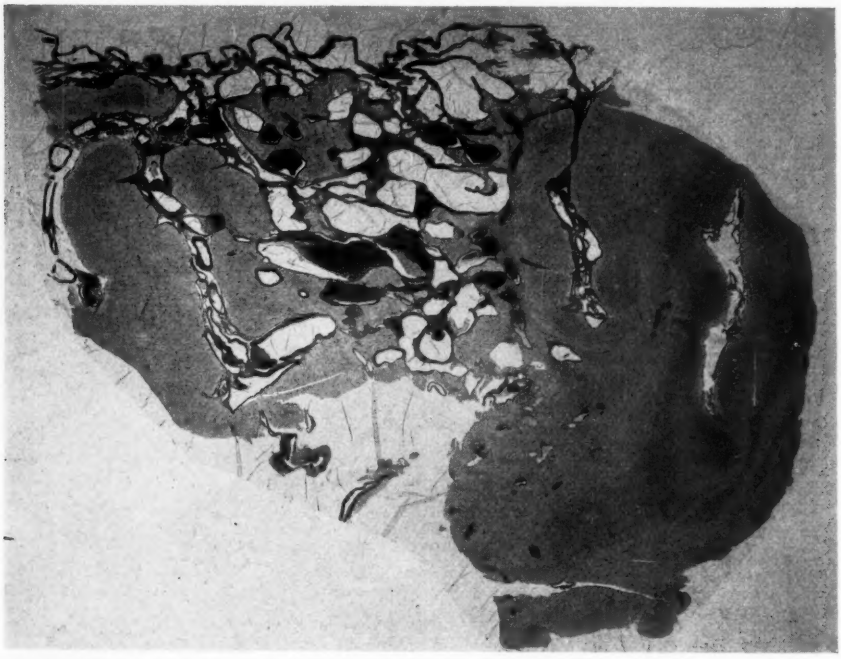

FIG. 6. Histologic section through arteriovenous malformation. The lower portion of the cerebral-vascular cone is not included.

sembling pure hyalinized collagen. Some vessel walls contain calcium granules, and rather large masses of this substance may be found in areas of old hemorrhage.

The perivascular white matter is arranged loosely, since the vessels, distended during life, have collapsed. The persisting cerebral tissue is altered in its relations both to blood vessels and to the adjacent widened perivascular spaces.

Preoperative and antemortem hemorrhages occur usually on, or quickly extend to, the looser, buried periphery of the mass. Gillingham[4] noted that such hemorrhages track toward the ventricle, and considered that blood found in the spinal fluid usually comes via the ventricle rather than the subarachnoid space. Mackenzie[7] believed such small hemorrhages a more common source of neurologic symptoms than the shunt-produced anoxia postulated by Olivecrona and Riives.[9]

Spontaneous thromboses may be found in smaller vessels, but only rarely are they extensive. Older writers, including Dandy,[3] who chiefly described lesions following death of the patient, were more impressed with thromboses than are those of the present. Occasionally they may progress and gradually obliterate the lesion. Potter[11] described a case in which a typical arteriovenous malformation was photographed at operation and not removed. At necropsy 6 years later an experienced pathologist was unable to find evidence of any vascular abnormality. Cushing and Bailey[2] described a lesion that became obliterated by thrombosis and fibrosis following surgical exposure and radiation.

ORIGIN AND DEVELOPMENT

The congenital origin of arteriovenous malformations has long been suspected. In her accounts of the development of the cerebral arteries and veins Padget[10] detailed the embryonic courses of the developing vessels and pointed out mechanisms for the congenital origin of arteriovenous malformations, as well as explanation for the multiple arterial supply of so many of them. The anterior cerebral artery supplements the supply of the choroid plexuses in embryos prior to the formation of the corpus callosum and in adults this connection often persists as pial anastomoses between the anterior and posterior cerebral branches. She described a specimen in which the conspicuous posterior choroidal artery curved superficially and was intimately attached to its companion vein of equal size over the choroid plexus which is relatively enormous at this stage of development. These vessels are separated by only a double layer of endothelial cells, and she noted that a fistula here could explain the case of Jaeger and Forbes[6] and the probably similar case of Graf.[5] A fistula between choroidal vessels could involve the middle cerebral artery via the embryonic tentorial sinus. Yates and Paine[14] found the basis for the complicated drainage from a lesion of the posterior cerebral artery in persistence of the fetal vena capitis lateralis, caused, they believed, by the abnormally large amount of blood poured through it by the artery, with no intervening capillary bed. Padget noted that in embryos of

20–40 mm., the cerebral hemisphere is a thin shell except where the corpus striatum has appeared. The primitive capillary bed on the medial and lateral pallial walls, especially caudally, is supplied by the terminal pial branches of the anterior and middle cerebral arteries and drains through ill-defined tributaries into a plexiform marginal sinus. Fistulas between veins and arteries at this stage would explain lesions supplied by arteries widely separated at their origins in the adult state.

Ordinarily capillaries intervene between the arterioles and venules and friction of blood flow through their narrow spaces over a relatively enormous area provides the normal cerebral vascular resistance. In an area where this resistance is lacking, the fistula becomes a "parasite on the circulation" as Potter termed it. When the fistula exceeds a critical size and offers a path of less resistance to blood flow than through the normal capillary bed, the artery must dilate to bring more blood to the lesion and the veins must dilate and become tortuous to drain it away. Collateral vessels develop and dilate, adding to the mass of involved vessels. If small veins rupture in the malformation, a larger lesion, an aneurysmal varix, may be formed. This results in a wider shunt and progression of the lesion. Potter[11] showed an example of a small ruptured arteriovenous malformation demonstrated by angiography, having a small aneurysmal sac near the left posterior cerebral artery. The patient recovered from the attack. Seven weeks later, angiography showed the lesion much larger, its feeding artery, the aneurysmal sac, and its draining vein all increased in size. In such cases, either equilibrium is reached or the vessels stretch further or rupture again, repeating the cycle. The dilatation of the arterial trunk gradually extends backward toward the heart as the circulatory demand is increased. Norlén[8] proved quite conclusively that this arterial dilatation is secondary rather than primary, since it regresses to normal after obliteration of the shunt. These mechanisms of progression help to explain why originally congenital lesions may not become large enough to produce symptoms until childhood, or later in life.

Coexisting beside and adjacent to the arteriovenous malformation in histologic sections may be found normal-appearing (e, Fig. 4) arterioles, capillaries, venules and veins subserving circulation of the contiguous cerebrum. Apparently these vessels have no connection with the malformation. This adds support to the idea that the malformed area was originally and remains separable from normal brain tissue, intimating an origin of the malformation early in the development of the cerebral mantle. This leads to the reasonable assumption that enlargement of the lesion should take place between prescribed boundaries and does not require the gradual involvement of previously normal vessels, especially capillaries.

Appreciation is expressed to Dr. Lyle French of the University of Minnesota for providing the specimen described here, to Mrs. Sara Barnes, who prepared the histologic sections, to Mr. Lee M. Bowerman, Buffalo General Hospital, for the photography, and to the Buffalo General Hospital Neurosurgical Research Fund for financial assistance.

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LOCALIZATION OF BRAIN TUMORS AT OPERATION WITH RADIOACTIVE PHOSPHORUS

AN IMPROVED TECHNIQUE USING A PROPORTIONAL COUNTER*

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THE purpose of this paper is to describe the design, characteristics and use of a newly developed proportional counter for the localization of brain tumors at operation with radioactive phosphorus, P^{32}. The substitution of proportional for Geiger-Müller counting has made it possible to construct brain-probing counters which are mechanically and electrically superior to those that have been available.

The method of localization is based on the finding of Selverstone and Solomon in 1947 that P^{32}, after intravenous injection, concentrated more in intracranial tumors than in normal white matter by a factor of 5.5 to 11?.† They proposed in 1948 the use of a "minute counter constructed after the fashion of a ventricular cannula" for locating deep brain tumors.[11] Radioactive phosphorus proved to be ideal for the purpose, since its pure beta emission has an average range in tissue of about 1 mm. Research begun elsewhere by Robinson and Peterson[6] resulted in the development and construction in 1948 and 1949 of suitable 3 mm. and 2 mm. beta-sensitive G-M counters by Robinson,[5] in collaboration with Selverstone. Subsequently, successful use of the method was reported by Selverstone with various collaborators,[8,9,12,14,15] Morley and Jefferson,[4] Garrity and Matthews,[2] Schneider *et al.*,[7] and Matera *et al.*[3] Using the standard Robinson-Selverstone, 2 mm. G-M probing counter‡ and P^{32} injected intravenously, a positive test with tumor-to-brain activity ratios of 5 or more has been obtained in 96 per cent of a series of 232 operations for brain tumor.** Most of our failures occurred in those few cases in which a glioma was so diffuse that no normal control area was exposed for probing, or in which injection of P^{32} had been inadvertently delayed until just before operation. Possibly because we are

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† A study of the mechanism of this differential uptake of P^{32} has been made by Selverstone and Moulton,[10] by measurement of specific activities of tissue fractions. Steinberg and Selverstone[16] have studied the distribution of P^{32} in tumors and brain by radioautography.

‡ Manufactured by H. W. Leighton Laboratories, Inc., Hatboro, Pa.

** In 84 additional cases, radioactive potassium, K^{42}, has been used alone or with P^{32}, with similar results.[13,15] Radioactive sodium, Na^{24}, proved to be valueless, since it did not concentrate in tumors.[10,13]

so well acquainted with the design and use of the 2 mm. G-M probes, these have not been a cause of failure in our series. There have been complaints, however, from competent users, that some of the counters were fragile and relatively short-lived, so that difficulties occurred in the routine use of the method.[1]

Although we have found the performance of the standard probing counters to be generally satisfactory for localization of tumors, occasional serious limitations in their use have been encountered because of the relatively great lengths of their sensitive regions and insensitive tips (8 mm. and 7 mm., respectively; Fig. 1C). We are reporting here the development and use of a

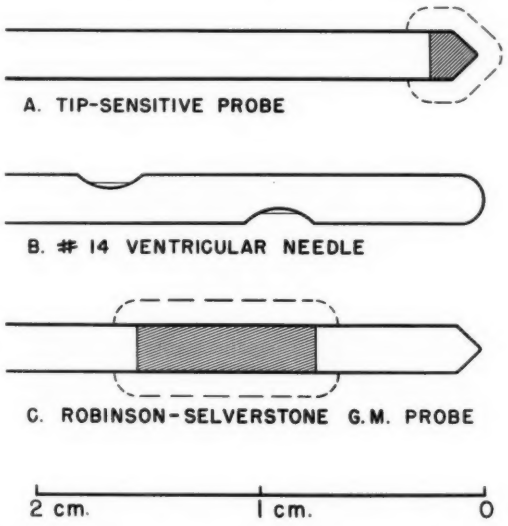

FIG. 1. Scale drawings of the ends of the new and standard probe counters and of a No. 14 ventricular needle. The shaded areas represent the parts that are sensitive to the beta-rays of P^{32}. The broken lines show the approximate volume of tissue counted by each probe.

proportional probing counter whose sensitive region is only 2 mm. long, and is located at its extreme tip (Fig. 1A). It is sturdier and longer-lived than the G-M probe. Its construction presents no unusual difficulties; one of us (C.V.R.) has built 7 of the new probes, of which 2 have been in use for more than a year.

DESCRIPTION

The new counter (Fig. 2) is similar in external appearance to the G-M probe. The cathode of the counter is a shell of stainless steel, 0.06 mm. thick and 2.1 mm. in diameter, with a conical end (total apex angle = 82°) whose point is slightly rounded (Fig. 3a). The anode (Fig. 3b) is a loop, 0.7×1.3 mm., of 0.007 mm. tungsten wire, mounted in a 0.25 mm., cupro-nickel tube. Fig. 3c shows the anode in air with a high voltage applied. The resulting corona-discharge is confined to the end-portion of the loop which coincides with the beta-sensitive region of the counter.

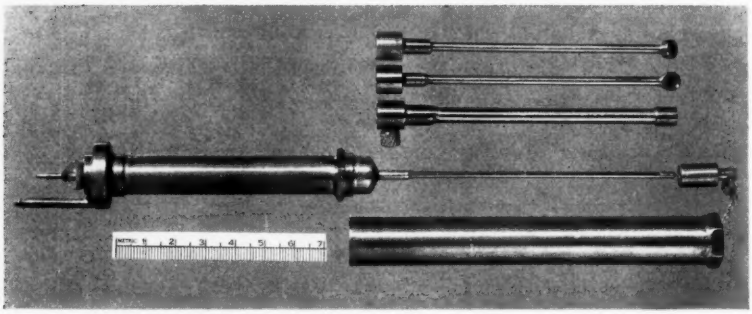

FIG. 2. The new tip-sensitive proportional probe counter, with (bottom to top) screw-on guard, test source, and 3 beta-shields, with openings at different angles.

This region communicates through 9 cm. of No. 14 needle tubing with a reservoir which also serves as a handle. The counter is evacuated and filled with diethyl ether at a pressure of 39.0 cm. of Hg.

A screw-on brass guard is provided for mechanical protection during sterilization and setting-up (Fig. 2). With the guard in place, no special care is required in handling the probe. The guard is open at its end in order to insure the penetration of steam during autoclaving, which can be done either with the main kit of instruments, or by "flashing" in the high-pressure autoclave. A U_3O_8 test source encased in a metal tube is attached to the guard and is sterilized with it.

A brass and Teflon connector similar to that used with the G-M probe connects through a 2-meter length of low-capacitance, teflon-insulated, coaxial cable to the amplifier input. The cable and connectors may be sterilized by autoclaving in the usual way; it is important that they be dry before use.

LABORATORY TESTS

Proportional operation differs from counting in the G-M range in that pulses are smaller (by a factor of 100 to 1,000) and are not of uniform size.

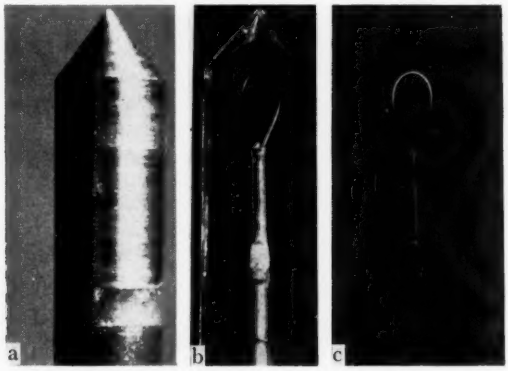

FIG. 3. Photographs of the tip of the proportional probe. (a) External view, (b) anode with cathode partly cut away, (c) anode during corona discharge in air.

Some degree of pulse amplification is therefore necessary, and a connecting cable and amplifier input of low capacitance are desirable. This counter is operated into a total capacitative load of approximately 110 $\mu\mu$f, and all pulses over 1 mv. (1.1×10^{-13} coulombs) are counted. Under these conditions, the relationship between counting rate and voltage is as shown in Fig. 4. An operating voltage of 1325 has been chosen. At this level, approximately half the pulses lie between 1 and 3 mv., with some pulses as high as 60 mv. After life tests of 2×10^{8} counts (approximately 4 times the life of the standard G-M probe), a drop of approximately 8 per cent in counting efficiency has been found, with no change, however, in the shape of the curve. As a

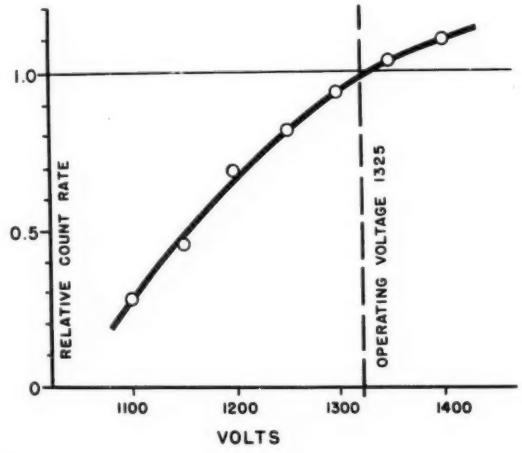

FIG. 4. Count rate as a function of voltage for the proportional probe counter (input threshold 1 mv., total input capacitance 110 $\mu\mu$f). A Model 182 (Nuclear-Chicago) amplifier-scaler was used for these measurements.

function of the level of incident radiation, the response of the counter shows departures from linearity corresponding to a resolving time of 60 μsec. (less than 1 per cent loss below 10,000 c./min.).

With operating voltage set at 1325 and pulse input threshold at 1 mv., the proportional probe shows a 2 per cent rise in counting rate for a 1 per cent rise in voltage, and a 1 per cent fall in counting rate for a 3 per cent rise in input threshold. Since proportional counters are most commonly used in applications where great precision is required, it is customary to specify unusually good stability of these circuit characteristics. The biological situation is so favorable here, however, with the 5:1 minimum ratio obtainable in the location of a brain tumor with P^{32}, that the precision available in standard commercial equipment is entirely adequate.

In order to test the new counter for accuracy in demarcating a simulated brain tumor, a 3-layer liquid system was set up, using carbon tetrachloride below, and diethyl ether above an aqueous layer containing P^{32} (Fig. 5). The

counting rates on entering and leaving the active layer for the proportional counter and for the standard Robinson-Selverstone G-M probe are shown. The depth in P^{32} is measured to the extreme tip of the counter in each case. Assuming a steady vertical displacement, the new proportional probe begins counting even before entering the active layer and quickly reaches its maximum rate, while the G-M probe does not begin to count until it has penetrated 4 mm., and then reaches its maximum more slowly. Similarly, even before the new probe leaves the active layer, it begins to show a fall in

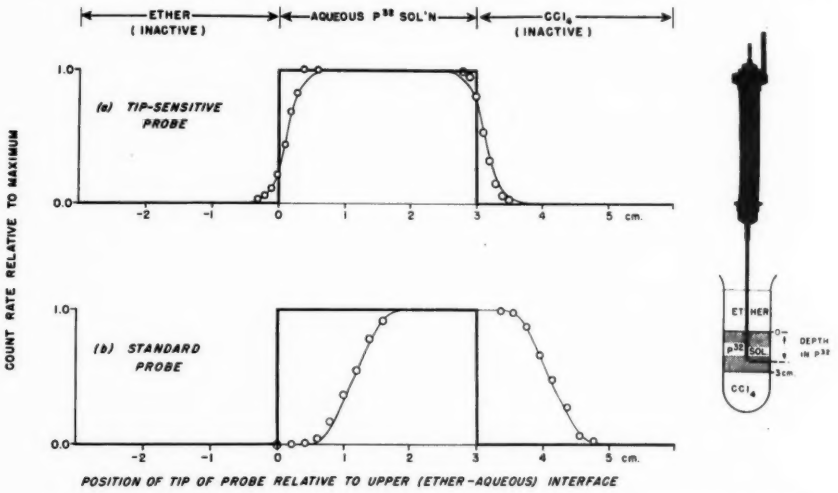

FIG. 5. Measurements of resolution in a 3-layer liquid system. A schematic diagram of the experiment is shown on the right. The maximum counting rates of the two counters in a solution with an activity of one microcurie per milliliter are 9,200 per minute for the tip-sensitive probe, and 31,700 per minute for the standard probe. These figures are in the approximate ratio of their sensitive volumes.

counting rate, which then drops rapidly to background. The counting rate of the standard probe begins falling only after it has entered 4 mm. into the inactive layer, and then drops slowly. Thus, the count-rate plot of the proportional probe approximates the true plot of P^{32} activity much more accurately than does that of the G-M tube.

In Fig. 5, experimental points (represented by circles) are shown together with theoretical curves which are based on the following assumptions: (1) exponential absorption of the P^{32} radiation, with a half-thickness of 1 mm.; (2) a sensitive length for the new probe of 2 mm., centered 1.2 mm. from its tip; and (3) a sensitive length for the G-M probe of 8 mm., centered 11.5 mm. from its tip; i.e., with 7.5 mm. of insensitive probe beyond the sensitive length. The curves for entry and exit of a theoretical point detector are almost identical with those for the tip-sensitive counter. Thus the new counter is effectively a point detector for P^{32} in the brain, and a smaller counter would provide no significant improvement in resolution.

CLINICAL USE

The patient receives a dose of from 0.1 to 2.0 mc.* of P^{32}. On the following day,† the sterilized counter and cable are set up in the operating room and connected to the amplifier-scaler.‡ The high voltage is set at 1325, and the proper counting rate at this voltage is verified with the test source. The background rate without the source is also checked and is ordinarily less than one count per minute. The craniotomy is performed, and counting rates

TABLE 1

Counting rates and ratios found with P^{32} and the new proportional probing counter in the first 10 cases

Patient	Age (Yrs.)	Dose, mc.	Time in Hrs. after Injection	Counts per Minute			Counting Ratio Tumor/White	Tumor Type
				Normal Brain		Tumor (max.)		
				Gray	White			
M.S.	2	0.1	5.0	7.5	2.5	134	53.6	Medulloblastoma, cerebellar
F.S.	51	2.0	22.0	12.5	10.0	730	73.0	Astrocytoma, frontal
C.M.	6	0.11	24.0	2.5	5.0	128	25.6	Medulloblastoma, cerebellar
A.H.	47	2.0	15.3	60.8	93.5	1158	12.4	Meningioma, temporal
R.D.	40	2.0	28.5	40.0	30.0	570	19.0	Astrocytoma, frontal
E.K.	33	2.0	4.5	15.2	9.4	16.9	1.8	Astrocytoma, frontal
H.B.	44	2.0	5.5	22.5	9.5	813	85.6	Astrocytoma, parietal
R.H.	$2\frac{1}{2}$	0.1	25.0	5.0*	—	26*	5.2*	Astrocytoma, pons and medulla
F.B.	21	2.0	6.0	23.8	10.0	600	60.0	Astrocytoma, septum pellucidum
C.S.	24	2.0	18.3	7.5	5.0	470	94.0	Astrocytoma, parietal

* Surface counting only, with beta-shield; cerebellar gray matter is taken as normal.

for normal gray and white matter are established by probing a control area of the brain. The region suspected of containing tumor is then explored. Counts are made for from 10 to 30 sec. at each of a number of sites. When the probe enters the tumor, a much higher counting rate will be registered. Table 1 shows the counting rates in brain and brain tumor and the maximum ratios in the first 10 cases in which the new counter was used. These ratios are in the same range as those that have previously been found with the Robinson-Selverstone G-M probes.[8,9,11,12,14,15]

Depending upon clinical indications, the tumor may now be removed by suction, dissection, resection en bloc, or cerebral lobectomy. With any of

* Doses of 0.1 mc. or smaller are used in children. A sufficient dose for an adult is about 0.5 mc., but larger doses have been given in these cases since we are studying specific activities of tissue fractions.

† An interval of at least 12 hours is preferred between injection of P^{32} and operation. Although excellent results may be obtained with an interval of only a few minutes, they are not reliable before 12 hours in certain firm, avascular, low-grade astrocytomas, such as that of patient E.K. in Table 1, where the interval was 4.5 hours.

‡ A Model 162 (Nuclear-Chicago) has been used in the cases reported here.

these methods, the extent of the tumor may be mapped before, during and after its resection by inserting the tip of the probe into suspected regions of the brain. The tip-sensitive proportional counter is especially suitable for testing the cut surface of the brain for completeness of removal of a tumor. This may be done either by a shallow insertion of its tip (2 or 3 mm.) or by counting at the surface of the tissue with a beta-shield on the probe. Such a shield is needed in order to avoid counting beta-rays from nearby tissues, since the mean range of these rays in air is about 70 cm. (as compared to 1 mm. in the tissues). Surface counting is impracticable with the standard G-M probe because of its long sensitive region and insensitive tip.

A set of 3 beta-shields for the tip-sensitive probe is shown above the counter in Fig. 2. The 4 mm. aperture is placed at a different angle in each shield, so that at least one will permit the counter to be used against any part of the exposed brain. Surface counting is useful not only for testing a cut surface, but also for verification of a tumor of the pons, medulla, optic nerves or other regions where insertion of a probe might produce significant neurological damage. For example, in a child (R.H., Table 1), who had received 0.1 mc. of P^{32}, the presence of an astrocytoma of the pons was verified by surface counting, with a ratio of 5.2:1. In another child (M.S., Table 1), surface counting of a medulloblastoma in the fourth ventricle was done, using the beta-shields, before further exposure of the tumor made it possible to insert the probe with safety. With 0.1 mc. of P^{32}, counting rates over six areas of the normal cerebellum did not exceed 3 counts per minute. Counting rates over different portions of the exposed tumor were 48, 52, 57, 58, 64, 66, 73, 80, 88 and 90 counts per minute.

SUMMARY

1. An improved brain-probing counter, sensitive only at its tip, has been designed, constructed and used for the localization of deep brain tumors at operation, with P^{32}. The counter operates in the proportional rather than in the Geiger-Müller range. It is more rugged and has a longer life than the Robinson-Selverstone G-M probe.

2. The sensitive part of the counter is approximately $2 \times 2 \times 2$ mm., which is small enough to permit the localization of P^{32} in tissues with an accuracy approaching that of a theoretical point detector.

3. The first 10 consecutive cases in which the new counter has been used are reported.

4. In use, the new proportional probe has the following advantages over the Robinson-Selverstone Geiger-Müller probe:

(a) Less penetration of the brain or tumor is required.

(b) Demarcation of the tumor is more precise.

(c) Counting with the shielded sensitive tip can be done on the surface of an exposed lesion. This is particularly useful in regions where probing would be unsafe.

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ARTERIOVENOUS ANEURYSMS OF THE SPINAL CORD

A REPORT OF TWO CASES INVESTIGATED BY VERTEBRAL ANGIOGRAPHY

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VASCULAR tumors of the spinal cord form, according to Merritt,[5] 4 per cent of spinal cord tumors. Some of these tumors are made up of actually growing tumor cells, others are congenitally formed anomalies of the vessels. To the latter belong the arteriovenous aneurysms. According to Wyburn-Mason,[14] Hebold[3] appears to have been the first to describe an arteriovenous aneurysm of the spinal cord. When Wyburn-Mason wrote his extensive monograph in 1943 on vascular tumors of the spinal cord he had found 14 cases in the literature and added 16 of his own. Since then, as far as we know, only a few more have been described. As the cases frequently offer difficult diagnostic problems and certain new views have been advanced during our investigation, we find it worth while to report the following 2 cases.

CASE HISTORIES

Case 1. A-n, L.J.V. A man aged 31 years was admitted to Serafimerlasarettet in July 1956. The first symptom occurred at the age of 10 years (1935), when a playmate accidently sat on his neck during a game. His neck cracked loudly and he suffered a violent pain at the base of the skull. He was unable to rise or to walk for several hours: the pain decreased, but his neck felt stiff. A week later he suddenly felt extremely severe aching in the back of the neck and vomited repeatedly during the succeeding week. Lumbar puncture showed blood in the cerebrospinal fluid. Roentgenograms of the cervical spine showed no abnormality. He was subsequently well until August 1941, when he suddenly and without known cause had pains and stiffness in the back of the neck. He vomited and remained at home for 2 weeks. During this period he noticed a little weakness and numbness in his legs. Two months later he again suffered aching and stiffness in the back of the neck. The pain now radiated out between the shoulder blades. It was observed that the optic discs were blurred and elevated about 1 dioptre. The patient was therefore admitted in November 1941 to the Neurological Clinic at Serafimerlasarettet.

Examination showed slight unsteadiness of gait, but otherwise nothing of note. An attempt at pneumoencephalography via cisternal puncture was interrupted when blood was obtained immediately. The patient had slight stiffness of the neck for a few days, and was then again symptom free.

The fourth, and thus far last, spinal subarachnoid hemorrhage occurred in 1947 after an accident when the patient was struck on the head by a plank. He was unconscious for a short period and subsequently somewhat dazed and stiff in the neck for 2 weeks.

Since 1943 the patient has had increasing weakness and muscular atrophy in the trunk and extremities. He first observed these changes in the left arm and leg. The

last year he had marked weakness in the right arm and leg also. He complained of slight paresthesia in the form of a sensation of pins and needles periodically in the right hand, but otherwise no impairment of sensibility. During recent months he had had difficulty with defecation and micturition.

State on Examination. The patient's general condition was poor and he was extremely emaciated. He breathed heavily with extensive use of the auxiliary respiratory musculature. Auscultation of the heart revealed a faint systolic murmur with a maximum at the base. The blood pressure was 120/80. Neurologic examination showed the cranial nerves to be normal. There was considerable spastic paresis in both the trunk and the arms and legs, with general muscular atrophy, which was most pronounced in the musculature of the shoulder and that of the left arm. The patient was a complete invalid because of his paresis, having to be lifted from his bed to a wheelchair, supported with pillows, etc. He showed slight impairment of sensibility for all qualities up to C4. The muscle reflexes were somewhat more lively in the left arm and leg with clonus of the left foot and positive Babinski's sign bi-

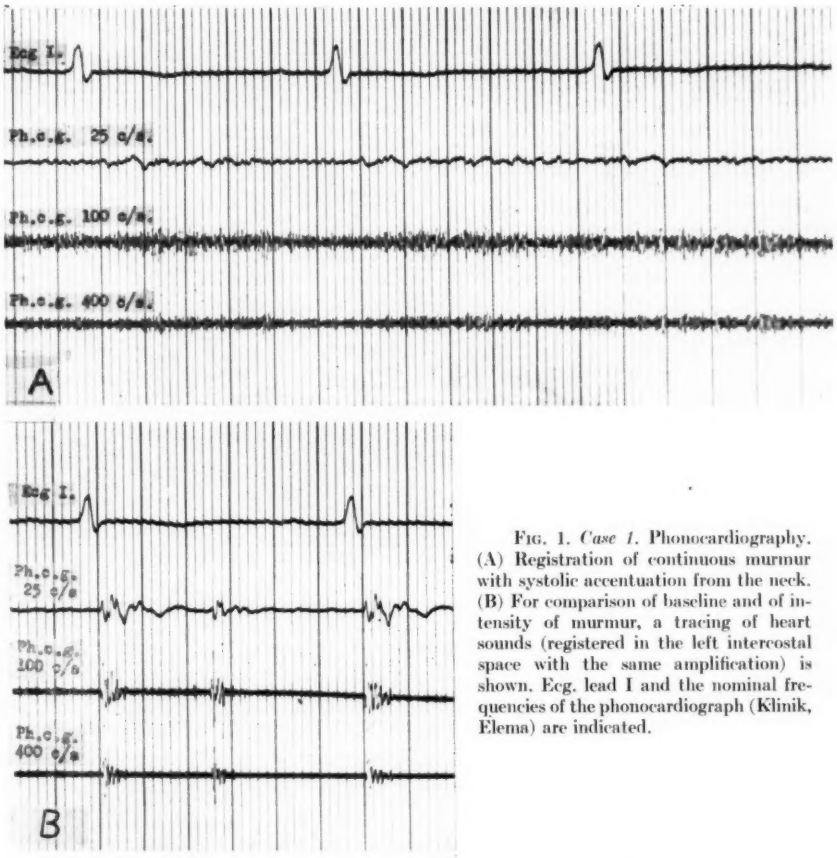

FIG. 1. *Case 1.* Phonocardiography. (A) Registration of continuous murmur with systolic accentuation from the neck. (B) For comparison of baseline and of intensity of murmur, a tracing of heart sounds (registered in the left intercostal space with the same amplification) is shown. Ecg. lead I and the nominal frequencies of the phonocardiograph (Klinik, Elema) are indicated.

laterally. The cerebrospinal fluid pressure was normal. Queckenstedt's test showed a slow rise of the cerebrospinal fluid pressure. The fluid was clear and faintly yellow; total protein was 80 mg. per 100 cc.; cell count was normal. Auscultation over the spine disclosed a loud, blowing murmur audible over the entire cervical region with a maximum in the upper part (Fig. 1). The murmur was also distinctly audible over the front of the neck, especially at the angles of the jaw.

Electromyography (first right dorsal interosseous and left extensor digitorum brevis) showed injury of the peripheral motor neurone.

Angiography (serial angiography of right and left vertebral arteries) showed the right vertebral artery to be considerably wider than the left. At the level of the 2nd cervical vertebra at the midline an irregular aneurysm, almost the size of a walnut, filled with contrast medium. The feeding artery was a branch of the vertebral artery arising at the level of the 2nd cervical vertebra. Greatly dilated veins drained the malformation, extending down to the inferior margin of the 4th cervical vertebra (Fig. 2).

Angiography (left common carotid artery) showed no abnormality. The posterior cerebral artery did not fill.

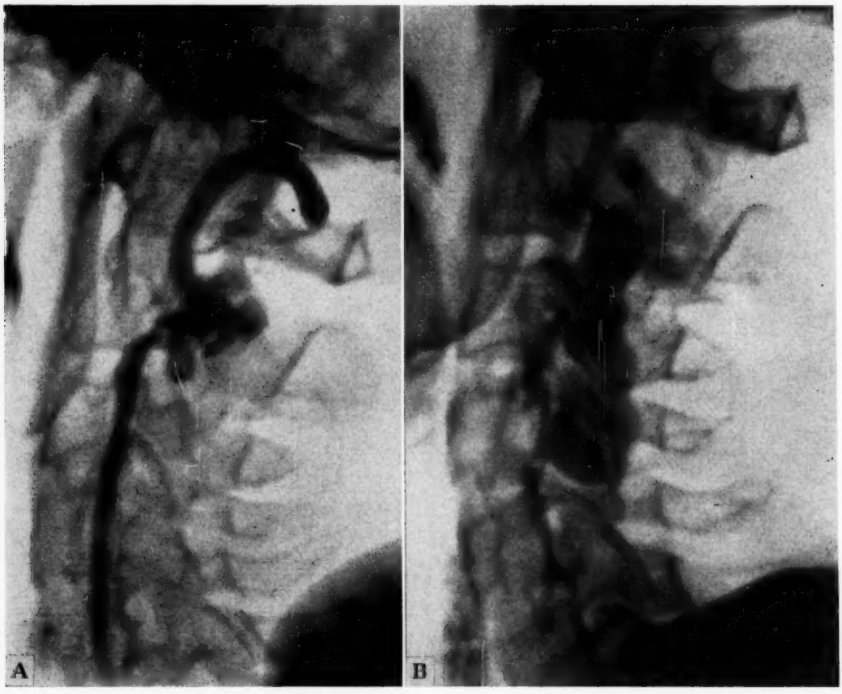

FIG. 2. *Case 1.* Angiograms of vertebral artery. (Interval between A and B was 3 seconds.) At the level of the 2nd cervical vertebra an irregular aneurysm, almost the size of a walnut and situated at the midline, filled with contrast medium. The artery feeding the aneurysm was a branch of the vertebral artery, arising at the level of the 2nd cervical vertebra. Greatly dilated veins drain the malformation, extending down to the lower margin of the 4th cervical vertebra.

Roentgenograms of the cervical spine and the lungs showed nothing pathologic. There was no possibility in this case, of course, of operative therapy.

Case 2. G-g, A-M. This patient was a woman aged 34 years. She had a history of good health until 1945 when she became acutely ill with aching in the head and back of the neck, with nausea and vomiting as well as stiffness of the neck. She did not lose consciousness. In direct association with this attack slight paresis developed in the right arm and leg and paresthesia in the right arm. Cerebrospinal fluid con-

FIG. 3. *Case 2.* Air myelography. From the level of the intervertebral disk between the 2nd and 3rd cervical vertebrae down to between the 6th and 7th the medulla is considerably thickened. The ventral outline of the middle and lower part of the cervical spinal cord is uneven and shows small indentations.

tained blood, with spiked club-shaped erythrocytes. The fluid was yellow after centrifugation.

During the succeeding years the paresis in the right arm and leg gradually increased, and paresthesias appeared in the right foot and the two ulnar fingers of the right hand. In November 1954 the patient had a new subarachnoid hemorrhage, with a feeling of heaviness in the head and interscapular pains with a sudden increase of both the right-sided hemiparesis and the paresthesias in the right hand and left leg. The paresis decreased within a month.

The patient was admitted to Serafimerlasarettet in February 1955.

Examination at this time showed right spastic hemiparesis, most pronounced in the arm. There was flexion contracture of the ulnar fingers. The entire right arm and especially the small muscles of the hand exhibited general muscular atrophy. The sensibility was moderately impaired for all modalities in the ulnar aspect of the right forearm and hand and the outer aspect of the right foot. The muscle reflexes

were increased in the right arm and leg, with Babinski's sign positive on the right. Left-sided carotid artery angiography showed no abnormality.

Air myelography showed a considerably thickened medulla from the level of C2 to C7 (Fig. 3). The sagittal diameter of the spinal canal in this region was increased. The ventral outline of the middle and lower part of the cervical spinal cord was uneven and showed small indentations. The diagnosis was an intramedullary expanding lesion. The patient was discharged and sent home with instructions to return within 1 or 2 months for operation.

The patient returned April 1955. *Angiography* of the left vertebral artery then

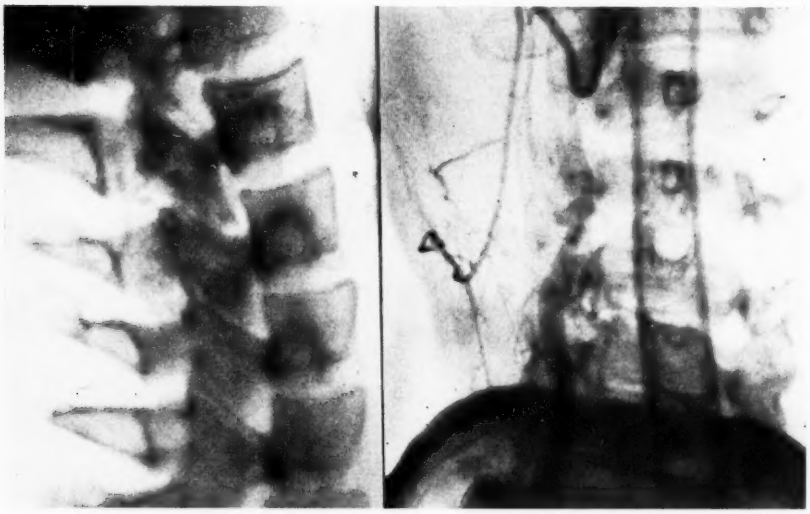

FIG. 4. *Case 2.* Angiogram of vertebral artery. At the level of the 4th to 6th cervical vertebrae abundant pathologic vessels in the spinal canal fill with contrast medium. As early as in the end of the arterial phase a vein with a diameter the size of a large knitting-needle, and situated somewhat to the right of the midline at the level of the 6th and 7th cervical vertebrae, fills with contrast medium.

showed at the level of C4–C6 filling of a mass of abnormal vessels in the spinal canal (Fig. 4). As early as at the end of the arterial phase a vein, with a diameter the size of a large knitting-needle, situated somewhat to the right of the midline at the level of C6–C7, was filled with contrast medium. The expanding lesion was in all probability a vascular anomaly (arteriovenous aneurysm).

Operation. Laminectomy of C4–C6 was performed. A large arteriovenous aneurysm covering the dorsal side of the spinal cord and extending down on its lateral aspect to the right was explored. The aneurysm consisted of arterialized veins up to the diameter of a goose quill. Radical removal was impossible and one had to be content with decompression.

Follow-up Examination in April 1957. There was slight subjective improvement during the months immediately following the operation, but later her symptoms became worse. More recently she had noticed weakness of the left arm and leg as well as imperative straining on defecation and micturition. No further subarachnoid bleeding had occurred.

Examination revealed atrophy of the small muscles of the neck and the muscles of the arms and hands, severest in the triceps, interossei and the thenar and hypothenar eminences. There was considerable paresis of the arms and hands, severest on the right side, and slight increase of tonus. There was moderate paresis of both legs, most pronounced on the right side, and severe spasticity. Tactile sensibility was diminished over the entire right hand and on the ulnar side of the left hand. Analgesia and thermoanesthesia were present on the left half of the body below the level of T4. The reflexes of the arms were slightly exaggerated, except for the right triceps reflex which was absent. The reflexes of the legs were greatly exaggerated. The Babinski sign was positive bilaterally.

DISCUSSION

Terminology. When Virchow classified vascular tumors in 1863, he called the group of vascular tumors that usually consisted macroscopically of large, dilated, tortuous vessels in arteriovenous communication through a mass of abnormal vessels which took the place of the usual capillary bed, "angioma racemosum arteriale." It was with a certain hesitation that this denomination was applied, and Virchow was aware that these tumors were not growing neoplasms in the usual sense, but of congenital derivation. Subsequent embryologic and pathologic research demonstrated that no other explanation is tenable. This group has since been given a series of different names, but these lesions today are usually termed arteriovenous aneurysms, arteriovenous malformations or angiomas.

There has frequently been discussion whether these malformations might be purely arterial or purely venous, and views on this have changed.

Notwithstanding the exceedingly thorough work by Wyburn-Mason, this problem cannot yet be considered satisfactorily resolved. Angiography should of course be one of the best means of determining the type of vascular anomaly, since it provides valuable information regarding the communications between the arterial and venous vessels. This has been demonstrated in the present study.

Symptoms. In our 2 cases there was a history of repeated spinal subarachnoid hemorrhage, and the clinical pictures agreed with those described by Wyburn-Mason, *inter alios.* Naturally it is often difficult to differentiate the spinal subarachnoid hemorrhages from the intracranial, especially if the source of the hemorrhage lies within the cervical spinal cord. If bilateral paresis or girdle pains occur, or especially if not only central but also peripheral paresis (compression of the anterior horn cells and/or roots) occurs, in connection with subarachnoid hemorrhage, spinal subarachnoid hemorrhage should be suspected. Tarlov and Keener,[12] *inter alios,* have called attention to the fact that spinal subarachnoid hemorrhage can be caused not only by vascular tumors and malformations but also, although more rarely, by other spinal tumors (sarcoma, ependymoma, neurinoma and others).

Diagnosis. Visualizing the spinal arteriovenous aneurysms with myelography is frequently difficult. In Case 2 the ventral outline of the spinal cord within the actual region was uneven and presented small indentations.

This picture is not of course characteristic of vascular malformation, and may occur with intramedullary tumors of various types. Such a picture in the presence of subarachnoid bleeding should, however, suggest a vascular malformation.

Attempts have been made with positive contrast medium (Lipiodol) in which, in certain cases, it has been thought that patterns of string-like contrast-free spaces could be visualized within the contrast medium, which would indicate the presence of pathologic vessels on the surface of the spinal cord.[2,9] Interpretation of these pictures is naturally extremely difficult in many cases.

Wyburn-Mason was of the opinion that the static Lipiodol picture was unable to provide diagnostic guidance. On the other hand, he described a technique by which under the roentgen-ray screen and by kymography in the partial hold-up of the oil it was possible to observe pulsations synchronous with the heart beat. We have had no experience with this method, however.

According to Mettler[6] the vertebral artery supplies not only the cervical spinal cord but also the upper thoracic segment down to D4. Consequently angiography of the vertebral artery is a suitable method for the investigation of cases of suspected vascular tumors or anomalies. The method used in our cases was that described by Lindgren,[4] with introduction of a catheter into the aorta or the subclavian artery via the femoral. It should be possible to visualize vascular anomalies located more caudally by means of aortography with filling of the intercostal arteries. We have not had a possibility to test this assumption thus far.

The possibility of carrying out interosseous angiography at the spinous process should be considered in these cases.

So far as we are aware, there are no reports in the literature of murmurs over the spinal column in these cases. As shown in Case 1, however, auscultation over the spinal column may sometimes provide valuable diagnostic information.

Treatment. Radical treatment of these aneurysms is naturally difficult if not impossible. There are, however, a few cases described in which extirpation was done.

Scoville[10] performed total extirpation of an arteriovenous aneurysm in the region of the conus in a 14-year-old boy. This aneurysm, among other effects, had caused erosion of the 12th thoracic vertebra. After laminectomy the aneurysm swelled to such an extent that the surgeon was forced to perform the extirpation as there was danger otherwise that the aneurysm would burst. The anterior spinal artery was also ligated. The operation was succeeded by paraplegia, but at follow-up examination 6 years later extremely good restitution was observed, and the patient was able to walk without notable impairment!

In this connection we should also mention Tarlov's[11] extirpation of a spinal extradural vascular tumor, which proved to be a hemangioblastoma. During the operation he injected Diodrast directly into this vascular

tumor, making it possible to determine the course of the feeding arteries and draining veins. In his opinion this greatly facilitated the extirpation.

Irradiation therapy has also been suggested, but would undoubtedly have just as little effect on the spinal arteriovenous aneurysms as it has been reported to have on the cerebral.[1,7,8,13]

SUMMARY

Two cases of arteriovenous aneurysm of the spinal cord are reported. In both cases the diagnosis was confirmed by angiography of the vertebral artery. In one case auscultation revealed a loud murmur over the spine.

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THE PREVENTION OF EXPERIMENTAL CONTRAST MEDIUM INJURY TO THE NERVOUS SYSTEM*

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THE development of new roentgen contrast agents has made individual angiographic procedures safer. However, this advance must be weighed against the continually widening use of diagnostic angiology and the increasing demand for greater roentgen contrast in these studies. It is our considered opinion that there is probably no known contrast agent that is not capable of producing a necrotizing lesion if it reaches the vascular bed of an organ in the mainstream of its flow in a concentration approaching the high initial level required for angiography. Because of this element of danger inherent in modern diagnostic angiology the prompt reporting of experimental studies demonstrating a dramatic protective effect against contrast medium injury to the central nervous system is warranted, despite the fact that a complete understanding of the mechanism of the protective action has not yet been attained.

EXPERIMENTAL

The methodology, including the site of test, the toxic roentgen contrast agent, the criteria of injury, and the quantitative grading system has been previously described.[4] In brief, the rapid injection of a 1 cc. per kg. dose of 70 per cent Na acetrizoate (Urokon) into the aorta via a retrograde femoral artery catheter will produce a predictable toxic reaction. This injury is characterized by a severe tonic-clonic spinal convulsion, a permanent paralysis of the hind limbs, and a massive necrosis of the lumbosacral cord.

The theoretical approaches explored and the various agents and procedures used in seeking a protective mechanism against contrast medium injury are outlined below:

1. Protection against changes in circulatory dynamics:
   a. Autonomic ganglionic blockade—Arfonad (camphorsulfonate)
   b. Smooth muscle relaxation—Papaverine HCl
   c. Inhibition or lysis of thrombi—heparin and Varidase (Streptokinase-Streptodornase)
   d. Metabolic saturation of vascular wall—glucose

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2. Protection of neurones against primary toxic and secondary anoxic injury:
   a. Lowered metabolism—hypothermia
   b. Anticonvulsant activity—procaine HCl
   c. Provision of metabolic substrate for neurones—glucose

In these studies all agents were administered through the catheter in the femoral artery prior to the injection of Urokon. The volume and rate of injection were adjusted so that the primary circulation of these agents was through the vascular bed to be exposed later to Urokon. In Table 1 the therapeutic agents tested, including dosage, concentration, and time of

TABLE 1

Summary of protection tests against toxic effects of Na acetrizoate (Urokon) upon canine spinal cord

Agent	Dose per Kg.	Concentration Per Cent (w./v.)	Application Time* Min.	Number of Animals	Criteria and Grades of Injury and Number of Dogs											
					Convulsive Response				Neurologic Impairment				Anatomic Lesion					
					None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	0	1	2	3	4	5
Control (Urokon)				7				7				7			2	1	4	
Arfonad	0.04–0.15 mg.	0.001	2–9	5			3	2		1	1	3			1	1	1	2
Papaverine HCl	15 mg.	0.8	2.5–3.5	5			1	4		1		4			1	2	2	
Heparin	10 mg.	0.5	10–13	5			1	4			1	4				1	2	2
Varidase	125,000†	10 cc.‡	9–13	5			1	4				5				3	1	1
Hypothermia§				10			1	9	6		2	2		2	3	5		
Procaine	25 mg.	2.0	0.5–6	13	3	7	3		5	4	2	2		2	5	6		
Glucose	1 and 2 gm.	20.0	1	11	1	9	1		10			1	3	2	5	1		
Sucrose	2 gm.	20.0	1	5		1	2	2		1	2	2		1	1	1	2	

* Time administered preceding Urokon.
† Total dosage (made up in 10 cc. sterile saline).
‡ Total dose.
§ 27–29°C. during and for 1 hour following Urokon.

administration preceding Na acetrizoate, are listed. Sucrose was used in studies of the specificity of the effect of glucose. In most of the studies continuous arterial pressures were recorded through the aortic catheter using a Sanborn electromanometer. The tests were designed to evaluate high dosage levels of the agents tested, rather than aimed toward establishment of optimal doses. For an evaluation of the protective effect of hypothermia the body temperature of the test animals was stabilized at 27–29°C. before the injection and kept at that level for 1 hour afterwards.

RESULTS

The results of the tests are summarized in Table 1. The control animals showed a uniformly severe convulsive response, neurologic deficit and grade of anatomic lesion. In evaluating the degree of protection afforded by the various therapeutic procedures cognizance must be taken of the non-linear progression of the anatomic grading system,[4] with the sharp break between the mild injury of grade 2 (at most 5 per cent destruction of the lumbosacral cord) and the severe injury of grade 3 (30 per cent or greater destruction). Only with hypothermia, procaine and glucose was significant protection ob-

tained. The prophylactic administration of glucose, which protected almost all of the animals from severe injury, was clearly the superior of these three therapeutic approaches. This agent was equally effective in both 1 and 2 gm./kg. dosage schedules. Within the limits studied the time of administration of procaine preceding the injection of Urokon had no significant influence upon the results of the tests. When protection was obtained there was a good correlation between the degree of residual functional defects and the grade of anatomic lesions. Unlike the other therapeutic procedures hypothermia exerted a protective action despite the fact that the severe convulsive reaction was not eliminated.

DISCUSSION

In evaluating these results it is to be remembered that the final criterion of injury is not a transient disturbance in the blood-brain barrier, but a massive necrotizing lesion involving essentially the entire lumbosacral spinal cord.[5] The prevention of an injury of such devastating character to a tissue with such stringent metabolic requirements as the central nervous system by the simple approach of modifying the susceptibility of the test animal constitutes a major therapeutic achievement.

The mechanism of action of these protective effects is currently under investigation. Particularly worthy of study is the possibility that the major protective mechanism may be simply a shunting of the circulation from the cord to the periphery by means of a peripheral vasodilatation (procaine) or through an effect related to the tonicity or viscosity of the injected substance (glucose). The relationship of the degree of dilution of the contrast agent to the severity of injury has been discussed in detail elsewhere.[4] The lack of a protective action by drugs with a powerful vasodepressor action argues against the effect of procaine being a vascular shunt mechanism rather than a primary influence upon neuronal activity. The lack of a protective effect with sucrose suggests an activity on the part of glucose, based on the differential permeability of the blood-brain barrier, but does not allow a precise definition of its mechanism and locus of action. It is theoretically possible that this protective effect may be exerted primarily at a neuronal level. However, using stereomicroscopic observations of the vascular bed of the spinal cord in the living animal, employing a fluorescein-indicator method for the study of blood flow, we have demonstrated a severe and prolonged disturbance of the vascular dynamics of the spinal cord associated with the toxic reaction to contrast agents.[3] This observation strongly suggests the possibility of a direct effect of glucose upon the vascular bed of the spinal cord. Several possible explanations for such a vascular action, including saturation of the vascular endothelium or intercellular substance, an alteration of vascular dynamics through an effect of viscosity, or a specific metabolic interaction with enzyme receptors of glucose in the vessel wall remain to be explored; meanwhile certain implications of these observations emerge. The protective effect of hypothermia, which is far from complete and which has been attained only by a drastic alteration of the physiology of the experi-

mental animals, is primarily of academic interest. The stronger protective effect obtained by the prophylactic administration of glucose and procaine prior to the contrast agent is of more practical importance. If in the final analysis this protective action is determined to be dependent upon a vascular shunting mechanism, then the use of these agents to protect the central nervous system, particularly the spinal cord, during angiocardiographic and aortographic studies is evident. If any other mechanism of protection is demonstrated, then these same agents are applicable as protective substances during cerebral arteriography. That the scope of this protective action extends beyond the central nervous system is evident by the results of parallel studies[2] indicating that the toxic effect of contrast agents upon the kidney may be similarly modified. Glucose, being an innocuous agent, could be readily used as part of all clinical angiographic procedures. Until more is known of the physiologic effects of procaine employed as in this study, a cautious approach to the use of this agent is indicated. Certainly, in comparison to the large dosages required for protection in these studies the small amounts (3 to 6 cc. of 1 per cent procaine HCl) prescribed by Goodwin and Walter[1] against objective symptoms associated with angiography may be considered inadequate.

All of the incompletely resolved features of the protective effect, including mechanisms of action, and factors of dosage, route of administration, and time of application of the therapeutic agents are currently under investigation and other agents are being tested. Meanwhile a comprehensive paper is being prepared, describing in greater detail functional and anatomical aspects of the protective effect.

SUMMARY

The remarkable protective effect of glucose and procaine against experimental injury to the canine spinal cord by Na acetrizoate (Urokon) is reported. Theoretical considerations of the mechanisms of this protective action and the clinical implications of these observations are discussed.

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EDITORIAL

On March 14, 15, and 16, 1957 an International Symposium on the Reticular Formation of the Brain was held at and under the auspices of the Henry Ford Hospital in Detroit. Scientists representing various neurological disciplines from the four corners of the world were there to present and discuss their investigations. Much has been learned in the few years since it was first realized that the bulbar reticular formation is of great importance in controlling skeletal muscular activity, and that the more cephalad portions of this nondescript network of nerve cells and fibers are intimately concerned with the state of consciousness.

These investigations show the gross inadequacy for the understanding of neural activities of the few simple pathways with which the teacher orients the beginning student. All too frequently we get no farther either in our knowledge or our thoughts than these elementary and obviously inadequate, oversimplified charts of the nervous system. Paralysis and spasticity are erroneously thought to be the results of a "pyramidal lesion." Anesthesia or hypesthesia are looked upon merely as the result of interruption of certain sensory pathways. Such simple explanations often are not only inaccurate but are completely lacking in any explanation of the frequent changes in intensity of the various manifestations of relatively fixed disease processes. What of the facts that anxiety or attention increases the abnormal involuntary movements of various dystonias, or that concentration of attention elsewhere diminishes or abolishes the appreciation of painful stimuli? There is now definite evidence that the reticular formation is capable of increasing or decreasing the activity of some sensory end-organs such as the muscle spindles or the threshold of sensory perception. Furthermore, here is a mechanism concerned with the inhibition or facilitation of most neural activities, with the control of visceral and cardiovascular phenomena, and with the regulation of endocrinological activity.

This is a most complex mechanism, the study of which has just begun. No one not actively engaged in this investigation can hope to know or understand the many complex details of this intricate system. On the other hand, no one can enjoy a modern understanding of the nervous system who does not have a comprehension of the fundamental processes of the reticular formation. In order that the readers of the *Journal of Neurosurgery* may have a basic understanding of this important neural mechanism the Editorial Board invited Dr. J. D. French to prepare a special article summarizing our present knowledge of the reticular formation including the vast amount of new material presented at the symposium in Detroit. The Board is pleased to publish Dr. French's review in this issue.

*SPECIAL ARTICLE**

THE RETICULAR FORMATION

J. D. FRENCH, M.D.†

THE NATURE OF THE RETICULAR ACTIVATING SYSTEM

The Reticular Activating System Defined. Allen[6] considered the "formatio reticularis" as that mass of cells in the brain stem and spinal cord that is not utilized in the formation of motor-root or sensory-relay nuclei. In primitive phyla, this cellular mass represents the bulk of the entire central nervous system, but vertebrates, in which encephalization is highly developed, exhibit a marked expansion of reticular formation of the brain stem coincident with the appearance of cerebellar and cerebral hemisphere.[57] In its expansion, the reticular formation displaces sensory and motor neural structures laterally, surrounds or partially surrounds thalamic nuclei and becomes modified into such derivative masses as nucleus ruber, substantia nigra, subthalamus and other brain-stem elements.[6]

The continuum represented by the spinoreticular mass of interneurons is well illustrated by Abbie and Adey's[1] diagram of the nervous system of the frog (Fig. 1). The reticulothalamic portion of this neural mass begins in the bulb a little above the decussation of the pyramids and extends cephalad into the septal nuclei. Closely interrelated in function, hence considered as part of the reticular activating system, are the reticular formation, central grey, subthalamus, hypothalamus, and midline and intralaminar thalamic nuclei. At present, it is fruitless to review more extensively the cytoarchitecture of the reticular system for, while nearly a hundred nuclear masses have been identified in the reticular formation itself,[64] these collections of cells, with few exceptions, do not appear to represent functional units. It is appropriate to mention, however, that a distinction between caudal or reticular and rostral or thalamic portions of the reticular activating system is probably justified.

THE RETICULAR FORMATION

In the past decade there has developed one of the greatest booms in the history of neurology. The wastelands of the reticular formation, badly neglected except for an occasional enlightened glance since the time of Cajal, first became an active frontier in 1947 with the observations of Magoun and Rhines[58] and of Moruzzi and Magoun.[61] Subsequently, a huge literature has contributed such vast information about this centrally located brain-stem structure that it is almost impossible to keep up with its development. At the

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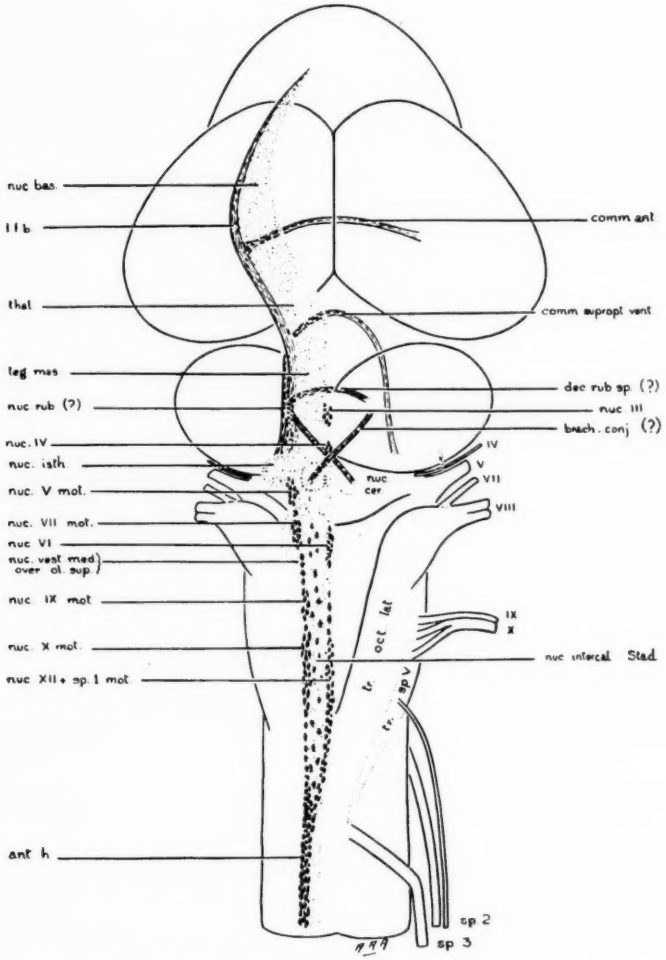

FIG. 1. This diagram of the frog brain illustrates the contiguity of the reticular formation with spinal interneuronal substance. (From Abbie and Adey[1].)

recent Ford Symposium, Sir Geoffrey Jefferson compared the reticular formation to a huge corporation which expands by buying up all its competitors: structures like the cerebellum, basal ganglia and hypothalamus seem to be disappearing successively into it. He added, perhaps a little wistfully, that the cerebral cortex now seemed to be considered by many only as a conveniently shaped object upon which to rest electrodes.

This meteoric rise in popularity of the reticular formation is justified for doubtless it is essential to, if not identical with, the vitally important in-

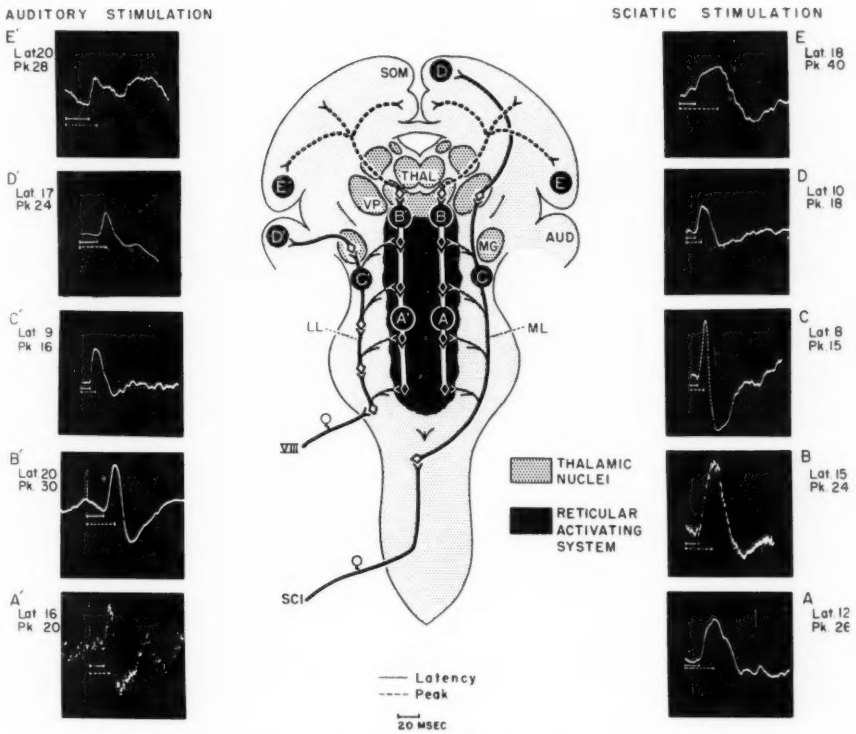

FIG. 2. The diagram of the nervous system shows the reticular formation in black. Primary sensory conduction is indicated by lines C-D for somatic sensation and by lines C'-D' for audition. Lines A-B and A'-B' indicate unspecific conduction in reticular formation through midline thalamic nuclei to diffuse cortical loci. Oscilloscope records indicate potentials evoked at designated site from auditory (left column) or sciatic (right column) stimulation. Notice prolonged latency (Lat.) and peak time (Pk.) for potentials evoked in reticular formation. (From French *et al.*[26])

tegrating structure that Wilder Penfield has proposed and called the "centrencephalic" system. Nuclear masses and fiber tracts in this small area relay and convey neural influences basic to the state of conscious awareness which enables man to react appropriately in his environment. Because of the importance of these brain-stem influences, it is considered appropriate to review them periodically and such an undertaking is attempted herein. This review will attempt only to epitomize a longer study published elsewhere[21] concerning the nature and function of the central brain stem known as the reticular activating system.

Sensory Inputs. Knowledge concerning the primary sensory systems is well established and a part of neurological orthodoxy. Each of these systems, from specific receptor through laterally situated lemniscal pathway to localized cortical receiving zone, is sensitive to a single modality of sensation and single shock stimuli are rapidly conducted throughout their extent

whether or not the subject is conscious. By contrast, the reticular activating system is responsive to stimuli applied to all sensory systems: a single electrode in the reticular formation or intralaminar nucleus of the thalamus, for example, will record alike (Fig. 2) pulses applied to sciatic, vestibular, auditory, and optic nerves (convergence). Moreover, identical neurons conduct these potentials of diverse origin since cells at a recording site in the reticular formation will not respond to a stimulus applied to one source immediately after they have been discharged from excitation of another system (interaction). These sensory potentials are known to reach the reticular activating system by direct connection with individual systems[60] or through collateral branches from each primary conduction pathway throughout the extent of the brain stem.[6,66]

Cerebral Inputs. Evidence linking the cerebral cortex with the reticular activating system is now available from anatomic[21,70] and physiologic[23] investigations. These cortical reticular pathways arise in discrete, well localized areas in the sensorimotor region, frontal and occipital oculomotor fields, cingulate gyrus, orbital surface, superior temporal gyrus and tip[23] and entorhinal cortex[3] (Fig. 3). Comparable to evoked sensory signals, responses elicited by excitation of each of these loci ("corticoreticular loci") are recorded throughout the extent of the reticular activating system, converge upon single electrode placements and interact, not only with signals from other corticoreticular loci but with shocks applied to sensory systems as well. This responsiveness to stimuli from such diverse sources is responsible for use of the terms "diffuse" or "unspecific" in describing the reticular activating system.

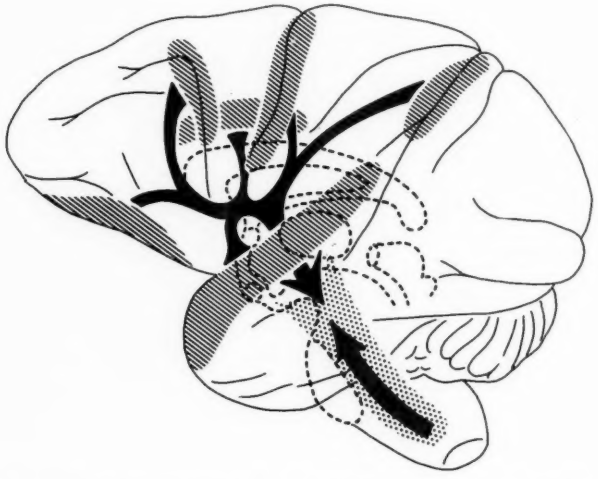

FIG. 3. The diagram of the monkey brain indicates cortical loci (hatched areas) which connect with reticular activating system (stippled areas). These "corticoreticular" loci are intimately related functionally with the reticular formation.

Other Reticular Activating System Inputs. Additional pathways of excitation of the reticular activating system are known to traverse the cerebellum, particularly its vermal and perivermal regions.[15] The superior cerebellar peduncle would appear to be implicated in transporting cerebelloreticular influences which are directed cephalically while fastigioreticular impulses through the uncinate fasciculus contribute largely to caudally oriented brain-stem mechanisms. Vestibular structures, formerly thought to function independently through the vestibulospinal tracts, are known to exert their major influence by way of reticulospinal pathways.[32] Similar concepts are proposed currently for the basal ganglia which have been connected functionally with the reticulothalamic system.[77]

Microelectrode Studies. Records made of responses evoked in single reticular neurons confirm and extend observations made in macroelectrode studies. Discharge of a single reticular neuron can be elicited by excitation of various sensory, cortical, cerebellar and brain-stem structures. While this convergence is widespread it is not absolute[75] since different neurons exhibit varied but consistent responsiveness to different sources of stimulus. A single pulse appears to excite some but not all cells within the reticulothalamic system indicating, perhaps, that each stimulus elicits activity in a precise constellation of brain-stem neurons.[41] The possibility of pattern responses such as these suggests that a degree of organization and specificity exists in the "unspecific" system as well as in primary neural structures.

Microelectrode studies indicate also that firing of single reticular cells can be inhibited by some stimuli and enhanced by others. Additionally, a unit can be made to increase or to cease firing by reversing a physiological stimulus: inverse vestibular excitation brought about by turning the head successively in both directions will elicit this response.[32] The progressive interest being displayed in mechanisms that inhibit as well as facilitate behavioral activity is advanced by such observations as these.

Neurohumoral Excitation. The recent studies of Dell and his associates[17] have indicated that neurons in the reticular activating system can be stimulated by the direct action upon them of physiological substances or chemical agents circulating in the blood as well as by neural inputs to the reticular activating system. Both epinephrine and acetylcholine are known to excite activity in reticular units[10,17] and comparable responses are elicited by adrenergic and cholinergic drugs.[11] In microelectrode studies, convergence upon single units from chemical and from electrical stimulation has been demonstrated. As will be discussed later, reticular activity elicited by neurohumoral stimuli is exerted both cephalically and caudally.

Reticular Activating System Conduction. Potentials elicited within the reticular activating system are conducted cephalically into the brain and caudally into the spinal cord. Anatomically, there is evidence to suggest that conduction in both directions occurs simultaneously as the Scheibels,[74] using Golgi techniques, have described axons which branch, sending one main division rostrad and the other caudad. Conduction within the reticular activating system generally is slow because of multisynaptic organization

but the versatility of this structure is indicated by the fact that it also contains larger fibers which transmit more rapidly.

Reticulocortical conduction is much slower than is transmission of impulses in the primary sensory system. Additionally, in contrast to specific pathways, reticular potentials are disseminated to widespread areas of cortex. This transport of "unspecific" influences is mediated in part by means of connections which the posterior part of the reticular activating system has with the anterior or thalamic portion of the system[43,69] and probably in part by direct or extrathalamic fiber bundles.[74,82]

Reticulospinal influences are conducted in fibers which course bilaterally from each side of the reticular formation and which are scattered throughout the lateral and ventral funiculi.[62] Transmission of these impulses is thought to be quite rapid.[29]

ASCENDING RETICULAR INFLUENCES

The Arousal Response. Two methods of assessment have been employed to study wakefulness and sleep. One method has utilized electroencephalographic techniques as a desynchronized tracing characterized by low-voltage fast activity is exhibited commonly during wakefulness and the wavy or synchronous tracing usually connotes sleep (Fig. 4). A second method of study relies upon behavioral responses of an animal to indicate its degree of wakefulness. In general, either of these methods is a reliable indicator of alertness but not invariably so. An example of paradoxical response is supplied by the atropinized animal which exhibits a hypersynchronous electroencephalogram yet is quite awake.[27] Despite such disparities as this (which may relate to selective blockade of acetylcholine activation of the reticular activating system), arousal or wakefulness will be used here to imply appropriate behavioral as well as electrographic responses.

Moruzzi and Magoun[61] first demonstrated that direct repetitive excitation of the reticular activating system induced arousal in the sleeping animal. Subsequently, it was adduced that electrical stimulation of a peripheral nerve or physiological excitation of a receptor system elicited arousal by energizing the reticular activating system and through it the diffuse reticulocortical projections: such excitation was accomplished by means of collateral inputs to the reticular activating system from primary sensory pathways.[22] Wakefulness can be elicited by stimulation of all sensory systems yet some, such as somatic sensory structures, are distinctly more potent arousers than are others such as the visual system.

Sustained Wakefulness. Arousal is induced generally by sensory activation of the reticular activating system and doubtless continued sensory inputs contribute to maintenance of the wakeful state. While cells in the reticular formation probably are capable of firing spontaneously,[17] such tonic basal activity is clearly unable at times to prevent sleep. The importance of sensory inputs in maintaining wakefulness is indicated by the fact that animals exhibit an alert electroencephalogram when the brain stem is transected up to but not beyond the sensory nucleus of the trigeminal

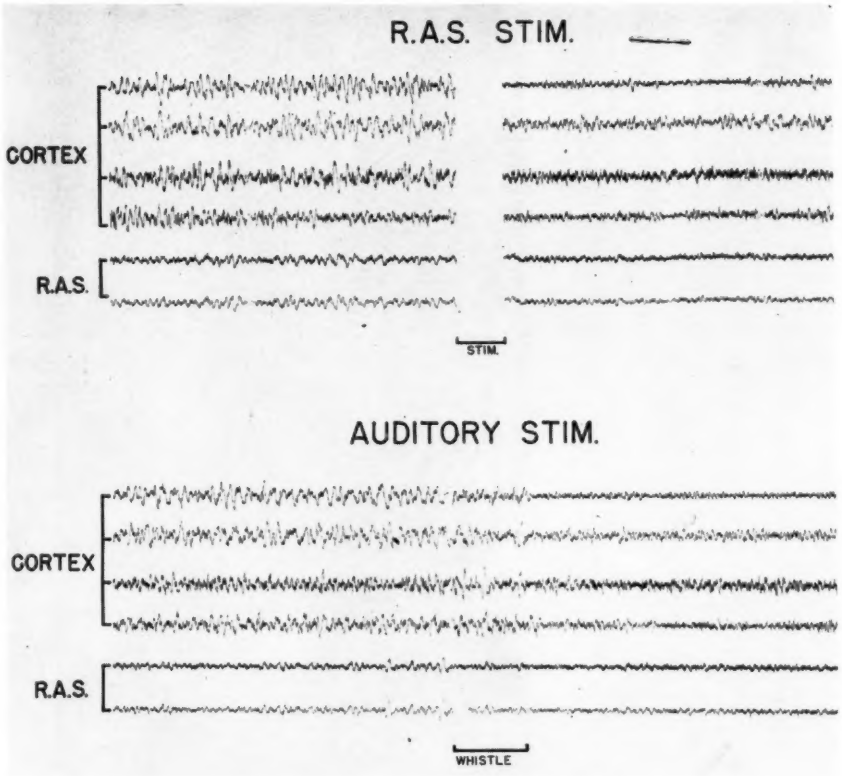

FIG. 4. The electroencephalographic tracings show abrupt transition from wavy record of sleep to desynchronized record of wakefulness to excitation of reticular activating system (upper tracing) and to physiological stimulus (lower tracing). (From French and King.[24])

nerve.[12] Similarly, an alert cat with a post-trigeminal transection will be rendered stuporous by division of the trigeminal nerves.[71] Clinically, remarkable mental aberrations were displayed by volunteer subjects placed in an environment that minimized sensory contacts.[39]

Probably inputs from corticoreticular loci to the reticular activating system contribute also to the alert state.[76] Arousal could be induced in normal, chronically prepared cats and monkeys by excitation of these zones[76] (Fig. 5). Additionally, the wakeful but inattentive animal would immediately exhibit behavior suggesting that it had become alerted when comparable surface stimulation was applied. As decorticate preparations are incapable of prolonged wakefulness or of attentive behavior, it must be presumed that corticoreticular loci are requisite to the mediation of these alert states.[23,76]

It has been proposed that neurohumoral mechanisms contribute to sustained wakefulness. Bonvallet *et al.*[10] suggested that arousal to noxious

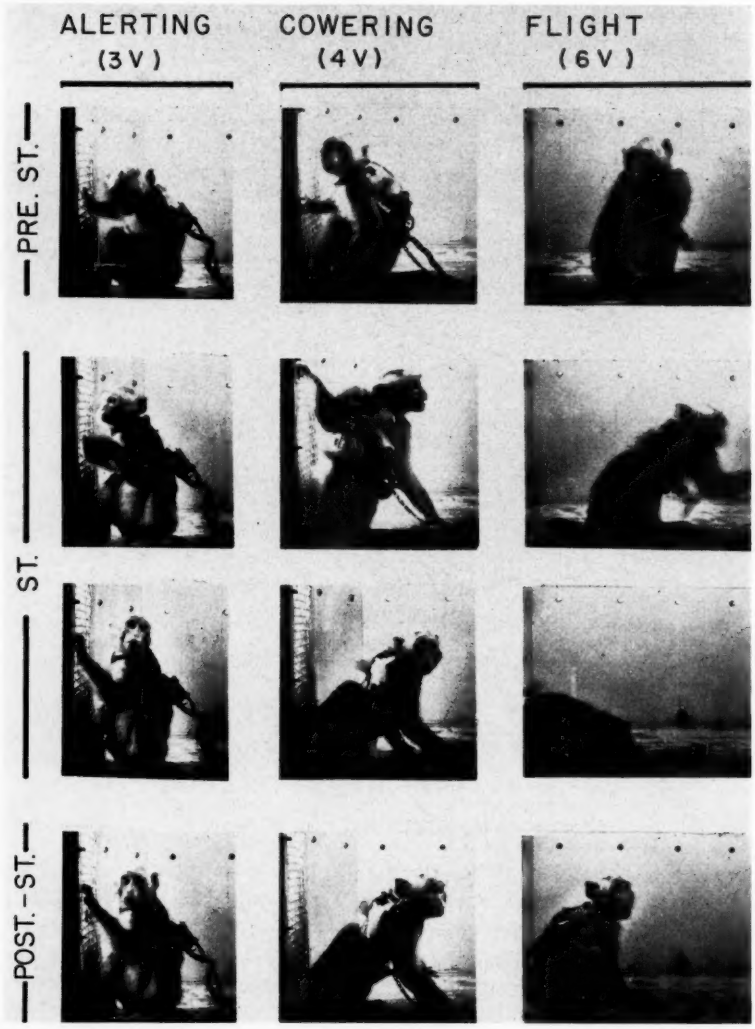

FIG. 5. Photographs of the monkey show behavioral responses of alerting (left column), cowering (middle column) and flight (right column) to stimuli of increasing intensity. Pictures in upper line were made before the stimulus was applied (PRE. ST.); those in middle two lines show behavior during stimulus (ST.) and those in lower line were taken after stimulus was stopped (POST.-ST.). Comparable results were noted from stimulation of corticoreticular loci. (From Segundo *et al.*[76])

stimuli has a dual etiology: the initial rapid response is thought to be mediated by neural excitation of the reticular activating system while slower developing epinephrine activation serves to perpetuate arousal.

Induced Sleep. Hess[42] has reported that sleep is induced in cats by pro-

longed slow stimulation of the midline thalamic nuclei. These observations indicate a significant difference in the physiological characteristics exhibited by the caudal and thalamic portions of the reticular activating system. Direct excitation of both loci with rapidly repetitive shocks induces immediate arousal. The application of slower pulses (5–10 c./sec.) to the reticular formation elicits only wakefulness while comparable excitation of the thalamic activating system induces diffuse electrocortical synchrony ("the recruiting response").[43] This synchronous response, presumably conducted by the same neurons that conveyed the more rapid desynchronizing influence, is comparable to the electroencephalographic rhythm of sleep. Apparently, therefore, the sleep induction reported by Hess is elicited when the thalamic portion of the reticular activating system is driven at a rate comparable to slow frequencies observed during sleep. Confirming this proposal are the observations of Akimoto *et al.*[5] who induced sleep in dogs by stimulating the diffuse thalamic system with 5 c./sec. pulses while 30–90 c./sec. bursts to the same region awakened the animals.

Anesthesia and Stupor. Some years ago it was proposed that transections of the brain stem at the collicular level produced coma because they deafferentiated the brain.[12] Now it is clear that the unconsciousness of decerebration results specifically from blockade of "unspecific" corticipetal influences rather than from total cerebral deafferentiation. Electrolytic lesions confined to the reticular activating system of cats and monkeys will induce permanent coma[25,50] while laterally placed brain-stem lesions which divide the long sensory pathways but spare the reticular activating system permit a continuation of the wakeful state.[50]

Reversible blockade of cephalic conduction in the reticular activating system by the administration of soporific drugs is known to account in large part for the induction of the anesthetic state. In Fig. 6 it can be seen that potentials evoked in the medial lemniscus by sciatic stimulation are unchanged during anesthesia while responses in the reticular activating system are obliterated by the drug.[24] Comparable blockade has been shown to account for the temporary stupor of concussion.[20] By contrast, excitant drugs such as amphetamine and epinephrine augment activity within the reticular activating system. Evidence is still fragmentary and somewhat conflicting concerning the action of "mood altering" drugs and "tranquilizers" but it is agreed that much of their effect results from altered function of the reticular activating system.[45]

Mental and Emotional Stability. In 1937 Papez[65] proposed that circuits from rhinencephalon through fornix, hypothalamus, thalamus, cingulate cortex and back to rhinencephalon were important pathways in the mediation of emotional behavior. More recent information linking the rhinencephalon functionally with the reticular system promises to contribute importantly to understanding of emotional problems and mental disorder.[2] It has been demonstrated that electroencephalographic arousal is manifested in the rhinencephalon by the appearance of synchronous waves rather than by a desynchronized tracing[37] and waves comparable to these have been re-

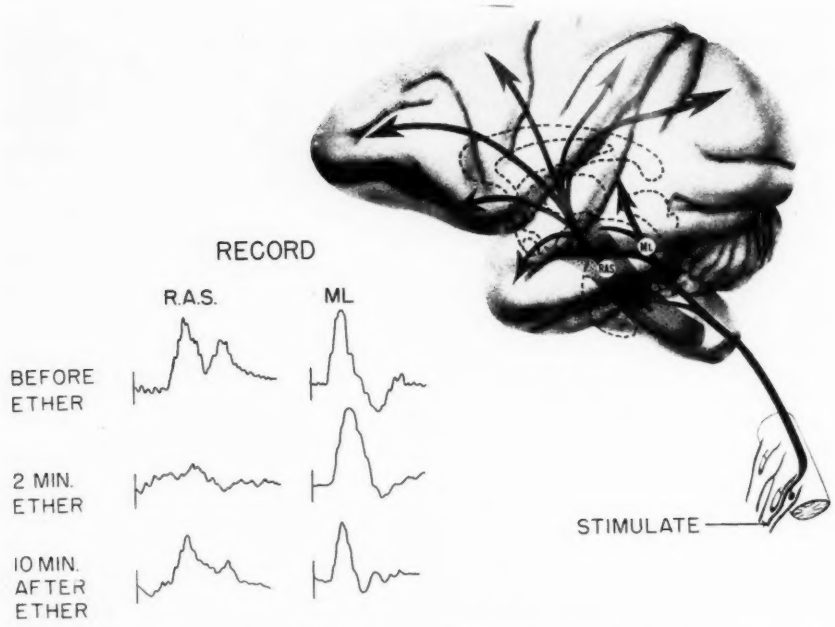

FIG. 6. The diagram on the right indicates recording sites in the medial lemniscus (ML) and in reticular activating system (RAS) to stimuli applied to a peripheral nerve. The records on the left show the potentials evoked in these two brain-stem areas before, during, and after the administration of ether to the monkey. Note that potentials recorded in the medial lemniscus are uninfluenced by the anesthetic agent while those recorded in the reticular activating system disappear soon after the application of ether only to return after termination of the anesthetic. (From French and King.[24])

corded in the temporal regions of children and psychopathic adults.[83] Doubtless rhinencephalic-reticular links participate importantly in disturbed mental states as well as in temporal lobe epilepsy.

DESCENDING RETICULAR INFLUENCES

The main reticulofugal influences which are expressed caudally are exerted upon the three principal divisions of nervous system function. The vital contribution of brain-stem structures to autonomic control and to neuromuscular function has been subjected to decades of investigation. More recent observations have indicated that the reticular system exerts powerful controls over sensory receptor and conduction systems.

Neuromuscular Modulation. The classical truncation experiments of Sherrington and Magnus indicated that, as transections were progressively lowered from the intercollicular level, spasticity became increasingly severe until the region of the vestibular nuclei was reached. Medullary transection below these structures terminated extensor rigidity and substituted instead a flaccid state. For this reason it was proposed that vestibulospinal facilitation accounted for the spasticity of decerebration.

In 1932, Allen[6] suggested alternatively: " . . . it might be explained that the section below Deiters' nucleus eliminated all or practically all of the connections of the formatio reticularis of the brain stem." Magoun and Rhines[58] later confirmed the correctness of this proposal. They were able to elicit inhibition of reflex and cortically induced movements by excitation of the medullary reticular formation and observed facilitation of these same responses by stimulating centrally located pontomesencephalic structures. Other observations suggested that stimulation of cortical "suppressor strips"[55] evoked motor inhibition by virtue of corticoreticular connections with the medullary inhibitory center.[56] Presumably, then, exclusion of these inhibitory corticoreticular inputs through decerebration enfeebled suppression and left unopposed augmenting reticulospinal influences. Infravestibular transection not only eliminated augmenting influences expressed by way of Deiterospinal pathways, but also amputated reticular facilitatory structures leaving intact only reticulospinal inhibition.

Originally, it was felt that inhibitory and facilitatory influences exerted by brain-stem stimulation upon segmental motor responses were nonreciprocal, affecting opposing flexor and extensor muscle groups alike.[58] Subsequent observations confirmed the existence of reticular stimulus sites inducing nonreciprocal responses but described, additionally, more numerous loci, excitation of which elicited reciprocal responses.[31] Presumably, nonreciprocal brain-stem activity contributes to tonic mechanism and to stabilization of joints during activity, while reciprocal loci obviously meditate movement.

Reticulopetal inputs exert a critical measure of control over the motor-modulating function of the reticular formation. The validity of proposals based upon the existence of "suppressor strip" has been challenged as originally enunciated[59,78] and these concepts now require modification. The "strip" areas, however, must contribute to motor control, for each one (8s, 4s, 2s, 18s, 24s) resides in or near a region described herein as a "corticoreticular" locus. Stimulation of some of these loci—the sensorimotor cortex, the frontal and occipital eye fields—elicit frank motor response, while excitation of other corticoreticular loci—cingulate gyrus, orbital surface—are said to inhibit motor activity.[76,79] It appears now that both facilitatory and inhibitory influences can emanate from some if not all of the corticoreticular loci.[21] The nature of the induced response doubtless depends on the type of stimulus applied and upon the local state of excitability displayed by responding cell populations.[51]

Reticulopetal inputs from other sources are important also in controlling motor activity. Midline and perivermal areas of cerebellum are known to exert both augmenting and suppressing influences upon reticulospinal mechanisms.[63,80] The vestibule not only supplies appropriate facilitatory or inhibitory impulses to the reticular formation depending upon the nature of the physiological stimulus delivered[31] but tonically energizes it, for section of the vestibular nerves results in diminution of the spinal myotatic reflex.[32] Spinal afferent inputs appear to supply similar reticulospinal en-

ergies as the relatively normal posture of the decerebrate frog is destroyed by posterior root section.[1]

The role of the basal ganglia in supporting reticulospinal motor activity is more obscure than is the contribution of any of the other structures mentioned. Both facilitatory[16] and inhibitory[49] properties have been assigned to these nuclear masses and probably either response can be elicited alternatively. Pallidospinal pathways have not been defined and it is probable that influences of the basal ganglia upon spinal motor mechanisms are exerted by way of the reticular system.

The Nature of Suprasegmental Influences. The reticular system appears to be able to act upon spinal motor (alpha) neurons through which muscular contraction is elicited or upon small efferent (gamma) neurons which connect with proprioceptor organs, the muscle spindles. The former influences are exerted primarily through internuncial satellite cells[52] and some of these interneurons appear to inhibit rather than enhance the excitatory state of the alpha neuron.[67]

It has been suggested that the rapidly conducting reticulospinal tracts set the stage for stimuli transported over the slower pyramidal tracts.[54] Whether or not this proposed relationship exists, pyramidal and reticulospinal functions doubtless are closely integrated. The reticular system exerts its influences cephalically as well as caudally and conceivably could act on spinal centers through the corticospinal tracts. Confirming this possibility is the observation that unit discharges which are synchronous with cortical waves elicited by stimulation of the reticular activating system can be recorded in the pyramid.[86] Moreover, the pyramidal tract apparently delivers its stimuli upon alpha neuron satellite cells in much the same way as do reticulospinal fibers.[53] These interrelationships and interdependencies have prompted one proposal that " . . . the now classical dissociation of pyramidal and extrapyramidal control of muscle is largely an artifact. Both mechanisms are found intermixed in the cerebral cortex and the reticular formation and localized in the cerebellum."[81]

Reticular control over gamma efferent activity, hence over the stretch receptor organ, has been recently established[35] and through such reticulospinal modulation, the myotatic reflex can be enhanced or inhibited. The importance of this control is suggested by Eldred *et al.*[19] who estimated recently that " . . . the range of bias at the command of the supraspinal centres is adequate to cover the whole physiological range of movement."

Spasticity. Spasticity results when the balance of facilitation and inhibition in reticulospinal output is disturbed in favor of facilitation. Such imbalance is induced by destruction of reticular inputs suggesting that, normally, reticulopetal influences are tonically inhibitory in nature. Spasticity is induced in animals when reticular inputs from the motor cortex, cerebellar vermis and striatum are destroyed: the effect is transient when these areas are removed individually and most extensive when all are eliminated together or successively.[49] Clearly, some of these reticular inputs serve to energize loci in the brain stem which contribute to reciprocal as well as nonreciprocal

activity, as loss of phasic movement is a prominent feature in spasticity. These effects are subject to marked phylogenetic variation for normal-appearing postures are retained in lower orders with the bulk of the brain removed while, in primates, severe disturbances result from cortical resection alone.

The spasticity of decerebration apparently results from tonic facilitatory inputs to the spinal cord, largely from suprasegmental levels, rather than from simple release of inhibitory control. As such suprasegmental influences are impossible in explaining the slowly developing spasticity of paraplegia, additional contributing factors must be sought. It may be proposed that a factor of release exists after spinal transection, for facilitatory influences residing in the spinal homologue of the reticular system are freed from suprasegmental inhibition (cf. Schiff-Sherrington phenomenon[72]).[30] Additionally, "short-circuiting" and diffusion of conduction potentials doubtless occur at the site of transection:[73] such artificial synapses have been demonstrated experimentally, in spinal cord[68] as well as in peripheral nerve.[36] Finally, ephaptic excitation[7] (nonsynaptic excitation of one cell by its neighbor) may be enhanced in paraplegia.

Tremor. Tremor comparable to the disturbance of parkinsonism is induced in animals by making lesions in the reticular formation[85] (although opinion[14] has been expressed that such lesions induce tremor by interfering

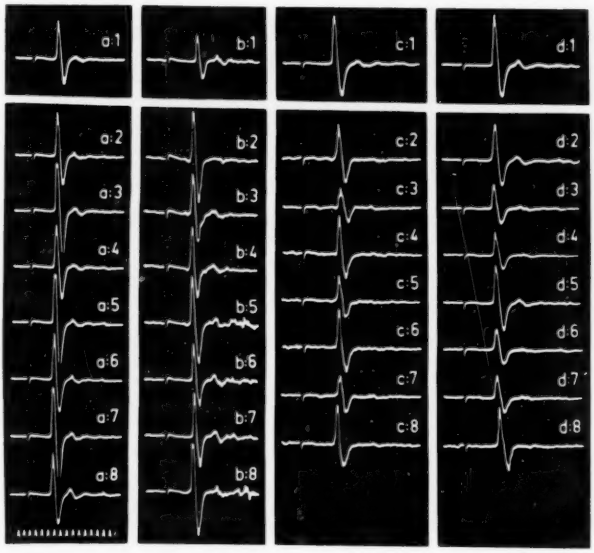

FIG. 7. Oscilloscope records of the monosynaptic reflex are shown. The upper lines are control responses. Remaining records were made during stimulation and show facilitation (left two columns) and inhibition (right two columns) which was induced by excitation of four different loci in the reticular system. Note particularly the rhythmic waxing and waning of the response in all columns. (From Gernandt and Thulin.[33])

with cerebellofugal pathways). As similar tremors can be elicited by stimulation of the reticular formation,[84] and as these tremors are opposed by anticholinergic drugs, it has been proposed that brain-stem lesions may cause cells in the reticular activating system to become hyperactive through sensitivity of degeneration.[84] This proposal implies that such hyperactivity in the reticular formation can exert a rhythmic discharge in spinal motor neurons and there is reason to believe that it can. Lloyd[52] and Kleyntjens *et al.*[48] have demonstrated that a reticular stimulus exerts a waxing-and-waning rather than sustained effect upon alpha neuron activity and such synchrony could doubtless be amplified by disordered brain-stem function (Fig. 7).

While abnormal reticular influences inducing tremor probably are conveyed directly to the spinal cord, transport through cortical relay may be involved additionally. Cortical reverberations traversing the reticular system may contribute to normal movement and some theories, notably that of Bucy,[13] consider these pathways implicated in the genesis of tremor (Fig. 8). Improvement induced by surgical attack upon pallidothalamic[16] or corticospinal[13,16] tracts would support this concept. Contrastingly it has been suggested that tremor results from direct reticulospinal defects but becomes apparent only against a background of tonic pyramidal activity.[57] This tonic influence would be eliminated by corticospinal division. It should be

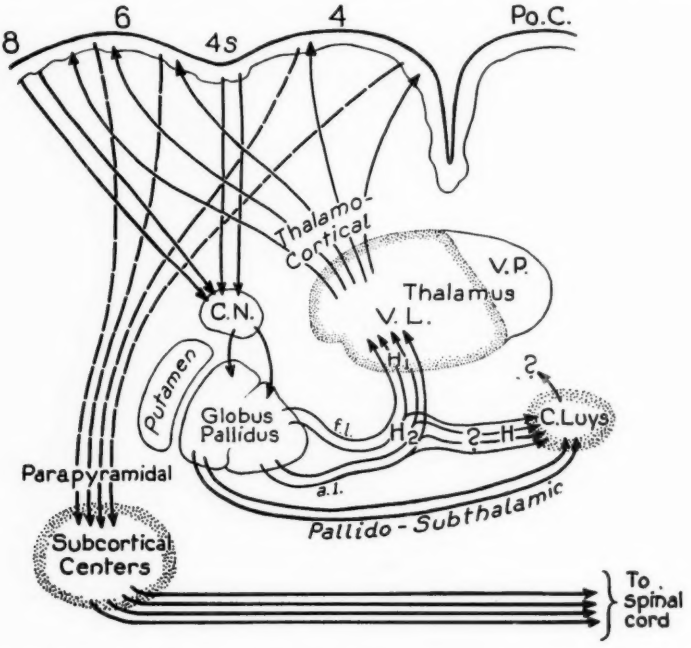

FIG. 8. This familiar diagram illustrates Bucy's proposal concerning cortico-reentrant pathways which may be disturbed in patients with tremor. It is probable now that the reticular formation should be added to the diagram. (From Bucy.[13])

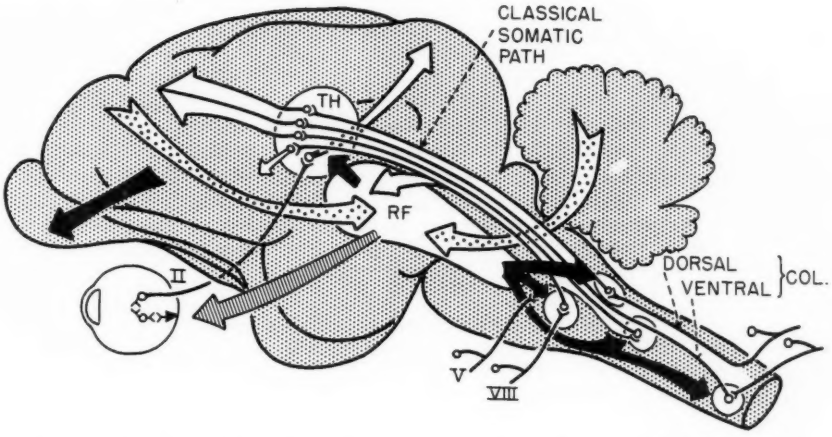

FIG. 9. This diagram of the cat brain illustrates the centrifugal influences which the reticular system (RF) exerts upon sensory inputs to the brain. The black arrows designate inhibitory responses which have been observed in spinal and brain-stem nuclear masses, in the thalamus and in the olfactory bulb. The hatched arrow indicates both facilitatory and inhibitory responses which have been described in the optic system. Arrows with heavy stippling illustrate comparable modulating influences which can be elicited by a cortical and cerebellar stimulation. (From Hernández-Peón.[19])

noted that the rate (10 c./sec.), regularity and time sequence of parkinsonian movements parallel at least one natural cortical rhythm, the alpha rhythm. Following brain-stem lesions such rhythmic influences, normally excluded from spinal neurons, might find restrictive barriers gone.

Control of Sensory Conduction. Since Granit and Kaada's[35] original observation in 1953, additional studies have indicated that the reticular system exerts extensive control over most, if not all, sensory pathways of the nervous system. Both facilitatory[34] and inhibitory[38] effects have been elicited although suppression appears to predominate. These controls, mediated by centrifugal fibers, have been demonstrated in cutaneous receptors,[47] muscle spindles,[35] cochlea,[28] retina[34] and olfactory bulb.[44] Reticular stimulation is known to modify afferent conduction particularly at relay nuclei: synaptic inhibition has been described in the dorsal root,[38] posterior column nuclei,[38] spinal V ganglia,[41] specific thalamic relays[46] and even in the reticular formation itself[4] (Fig. 9). That the entire reticular activating system contributes to this phenomenon is indicated by the fact that comparable effects are elicited whether the stimulus is applied to the reticular system or its corticifugal inputs.[4,38]

These phenomena would appear to explain the mechanisms utilized by animals and man in accepting certain stimuli and rejecting others. Certainly chaos would result if the nervous system was forced to recognize the overwhelming barrage of signals to which it is constantly exposed. Failure of this mechanism, indeed, may contribute importantly to mental disease. Additionally, functional disorders, such as the elusive trigeminal neuralgia, might well result from faulty receptive mechanisms.[47]

Autonomic Control. For the sake of completeness only, brief mention is made of the fact that numerous "centers" implicated in cardiovascular, respiratory, visceromotor, metabolic and temperature-regulating controls as well as with other autonomic mechanisms, coexist in brain stem with the reticular activating system. There is reason to believe, moreover, that these mechanisms are inseparable functionally from those relating to arousal, movement, sensation, etc. A stimulus from a single electrode placed in the bulbar reticular formation, for example, will elicit simultaneously changes in blood pressure, respiratory rate and reflex activity.[8] Polyphasic responses comparable to those resulting from stimulation of reticular formation[18] are elicited by excitation of corticoreticular loci.[9] Such integrating mechanisms as these underlie the mediation of pattern responses which are implicit in all levels of nervous system function but are most highly developed in cortical-centrencephalic systems.

SUMMARY

It has been possible to review here only in the most abbreviated manner the nature and function of the reticular activating system. The central brain-stem masses comprising this system are derivatives of a phylogenetically ancient column of spinocerebral neurons which are interposed between sensory nuclei and motor cells. Vertebrate encephalization has resulted in tremendous expansion of the rostral end of this structure and magnified extensively the ramifications of its function. Implicit in the mediation of these manifold functions of the reticular activating system are its interconnections with spinal cord, cerebral cortex, basal ganglia, cerebellum and vestibular nuclei and its response to humoral excitation.

Coextensive within the reticular activating system are systems which appear to exert influences that are oriented rostrally and others that are directed caudally. Principal among influences directed cephalically is that mediated by a diffusely projecting system of neurons which subserves arousal, sustained wakefulness and all the mental attributes of conscious awareness. Caudally oriented mechanisms include those that modulate muscle tone and movement, that control sensory inputs to nervous system, and that mediate processes of visceral regulation. Interference with cephalically directed influences results in mental disturbances, coma and the anesthetic state. Defects in caudally directed activity induce spasticity, tremor, and disturbances in motion as well as faculty preceptive phenomena.

The divisions of nervous system function enumerated above are entirely artificial and made purely for purposes of description. The evidence indicates rather that these several activities are so interdependent as to be inseparable since stimulation never elicits changes in one area of reticular function without inducing related change in all others. The reticular activating system, therefore, must be considered the great integrating mechanism of the brain without which unity of response to complex environmental stimuli is impossible. Investigation of its functions can be expected to extend knowledge concerning the intricacies of normal behavior. Doubtless in its dysfunction will be found the seeds of many nervous and mental disorders that currently plague man's understanding.

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CASE REPORT

SPINAL LITHIASIS

A CASE REPORT

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(Received for publication April 26, 1957)

Calcification within the neural axis may occur in a variety of conditions, usually associated either with local pathology such as calcified neoplasms or with systemic disease as in tuberculosis or parasitic infestation. However, the presence of calcification amongst the roots of the cauda equina is unique in our experience.

CASE REPORT

JHH #618989. J.P., a 60-year-old colored female, was well until one evening in July 1956 when vague lower abdominal pain developed and she was unable to void. She consulted her

FIG. 1. Anteroposterior and oblique myelograms of lumbar canal demonstrating one of the irregular filling defects (arrows) produced by the cauda equina calcifications.

personal physician who catheterized her and obtained 3000 cc. of urine. She was given some medication which relieved her discomfort and improved her urinary function for several weeks. However, her symptoms recurred and she was subsequently referred to the gynecology service for study.

Examination on admission revealed a thin, elderly colored female in no acute distress. Blood pressure was 180/100. There was moderate cardiomegaly with a grade 3 aortic systolic murmur. The abdomen was protuberant and nontender, and no masses were felt. Pelvic examination revealed atrophic external genitalia, post-menopausal mucosa, and a small atrophic uterus. Cultures of urine yielded a mixture of *Aerobacter aerogenes* and *Streptococcus faecalis*. Cystoscopy revealed an enlarged trabeculated bladder with evidence of chronic infection. An intravenous pyelogram was normal. The capacity of the bladder on cystometrography was 850 cc. with no sensation until 750 cc. was reached, and no contractions occurred. She was placed on tidal drainage and given appropriate antibiotics to control her urinary infection. After the infection was eliminated, she was given Urecholine, 10 mg. four times daily, and was discharged with an indwelling catheter in place, to be followed in the out-patient clinic. During the course of her out-patient follow-up, roentgenograms of the lumbar spine were normal. However, though lumbar puncture revealed normal pressure and dynamics, and a negative Wassermann, the Pandy was 4 plus and the protein was 97 mg. per cent.

FIG. 2. Operative photograph of the exposed cauda equina showing two of the stones intimately enmeshed in the medial roots.

2nd Admission. The patient was readmitted to hospital on the neurosurgical service, her bladder having remained atonic. In addition she had noted a loss of 13 pounds in weight and the onset of slight pain low in the back in the lumbar region.

Examination. Motor power and sensation were intact. Both ankle jerks and the right knee jerk were markedly depressed. Roentgenograms of the entire spine at this time revealed only moderate osteoarthritic changes, chiefly in the cervical region. Intravenous pyelogram was again normal. Routine blood counts were normal and the blood serologic test for syphilis was negative. The blood sugar and nonprotein nitrogen were normal. A myelogram revealed three irregular filling defects from L2 to L4 (Fig. 1), the nature of which seemed unusual. There was, as well, fairly marked cervical spondylosis.

Operation. On Dec. 14, 1956 a lumbar laminectomy at L1, L2 and L3 was performed. The bony canal and dura mater appeared normal. However, on incising the dura mater and arachnoid three large structures which had the appearance of hobnailed calculi of the bladder were seen to be enmeshed in the roots of the cauda equina corresponding to the myelographic defects (Fig. 2). These stones were intimately adherent to the roots and their tiny vessels, and could be removed only by sharp dissection. It was apparent that they did not arise from the arachnoid as do the familiar calcospheroids.

Course. Postoperatively she made an entirely uneventful recovery. The stones (Fig. 3) were found to be radiopaque. Qualitative chemical analysis revealed the presence of calcium, ammonia, magnesium and phosphate, there being no trace of carbonate, cystine, oxalate or uric acid. Postoperative chemistries of the blood gave the following findings: calcium 10.8 mg. per cent, phosphorus 3.5 mg. per cent, acid phosphatase activity 0.6 BU, and alkaline

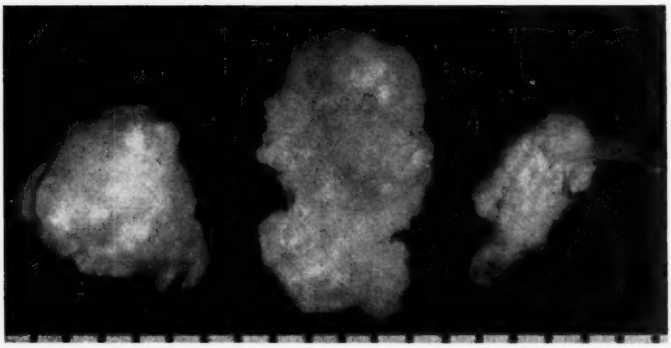

FIG. 3. Photograph of the specimens removed at operation. Note the small vessel attached to the specimen at the right. Scale in millimeters.

phosphatase activity 5.5 BU. Subsequent medical and endocrine evaluation has revealed no evidence of hyperparathyroidism or other abnormalities in calcium metabolism.

In the first 4 months postoperatively, there was no significant change in the patient's urinary status, aside from a decrease in the capacity of her bladder to 500 cc. She was maintained on constant urinary drainage to an artificial rubber urinal. However, on our most recent

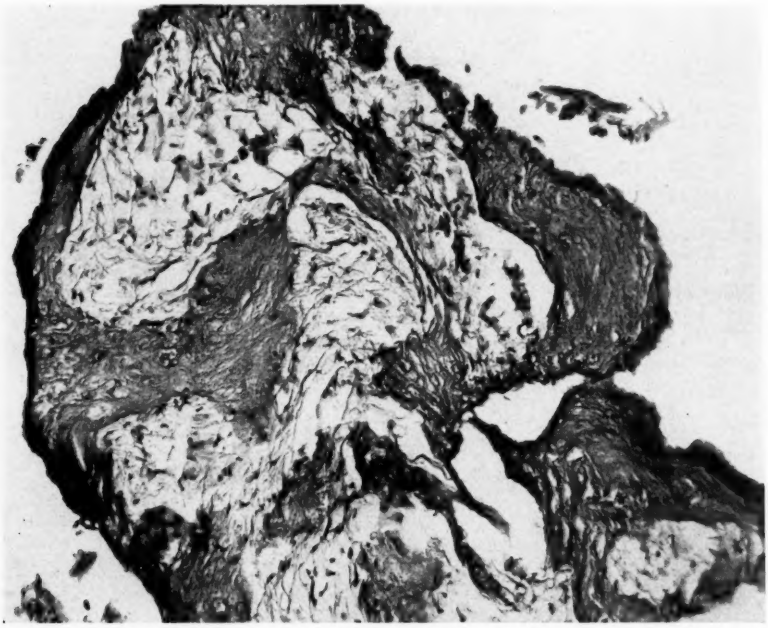

FIG 4. Photomicrograph of representative histological specimen (decalcified). Note dense fibrous stroma surrounded by laminated deposit of inorganic salts. (Hematoxylin and eosin stain, ×150)

examination, on April 23, 1957, it was found that she had normal bladder sensation and was able to void spontaneously without residual. Her catheter has been removed and she is now voiding normally.

Histological Examination. Sections of the decalcified specimen revealed the inorganic salts laid down in a somewhat laminated fashion in a dense fibrous stroma, not unlike the appearance of new bone formation (Fig. 4).

DISCUSSION

The presence of these calcified lesions in the cauda equina is difficult to explain. Whether they arose from tiny vessels accompanying the roots or from the sheaths of the roots could not be readily determined. It is the author's impression that they probably did produce the lower motor neuron paralysis of the bladder from which the patient suffered, by mechanical interruption of nervous transmission in the appropriate sacral roots.

SUMMARY

A case of intra-arachnoid calcified lithiasis of the cauda equina associated with an atonic urinary bladder is reported in a 60-year-old colored female. The condition is unique in our experience and no similar cases were found in a review of the literature.

BOOK REVIEW

THE VERTEBRAL VISUAL SYSTEM. By Stephen Polyak, late Professor of Anatomy, University of Chicago. Edited by Heinrich Klüver, Professor of Experimental Psychology, University of Chicago. *Chicago: University of Chicago Press*, 1957, xviii, 1390 pp., 551 illustrations, 27 of which are in color. Price, $45.00.

This is a remarkable book which has been published posthumously. It represents a lifetime of intensive scientific effort. The nature of the book is best expressed in the words of its author:

"The book is in four parts: historical, anatomical, pathological, and biological.

"The first part is an attempt to present the development of our knowledge of the bodily mechanisms underlying vision from the earliest efforts through the following ages to our own time. Historical investigation not only satisfied my curiosity concerning the origin of the concepts and ideas and their interaction but revealed both the temporal sequence of the discoveries and, more important, the ideological motivation for subsequent investigations. This was also the source from which the stimulus for my own research originated. This section is also intended to be a memorial to the many workers who gave us our present knowledge.

"The second part, the anatomical, describes the gross and fine structures which constitute the vertebrate visual system, principally in Man, Apes, and Monkeys.

"The third part deals with the pathoanatomical basis of disturbed vision, especially of the various visual field defects. This part may be helpful not only in understanding the pathology of vision, but it may also materially add to our understanding of the organization of the visual apparatus and its normal function.

"In the fourth part I discuss the intriguing problem of the origin and development of the vertebrate eye, how the eye may have initiated the formation of the brain, and how vision in turn has given an evolutionary impetus to the rise of the Primates, eventually culminating in the advent of Man."

The first section is far more than a history of the investigation of the visual system. It presents many of the aspects of the study of the entire nervous system, and even of biology. The photographs of approximately one hundred scientists who have been interested in this field are presented. Everyone interested in the history of medicine will find this section interesting and valuable.

The second section on anatomy is that with which the author was most concerned. It was as an anatomist that he approached this problem, and it is here that he deals with it most forcefully and most knowingly. However, this is not to belittle the remaining sections of the book.

The third section deals with human material. It is in reality a detailed anatomical study of twelve human cases in which either a neoplasm or a vascular lesion damaged or destroyed the visual neural pathways—particularly the visual radiations and/or the cerebral cortex bordering the calcarine fissure. These cases serve to illustrate the various functional and anatomical factors underlying visual disturbances. Their description and analysis are particularly valuable in view of the author's long-continued researches on the blood supply of the visual system. This, however, is the least complete section of the book.

The fourth section is concerned primarily with the comparative anatomy and physiology of the visual system. Here are to be found a most remarkable collection of photographs and drawings of the animals under consideration and their visual systems. This section emphasizes the importance of the visual system to the entire

organism, as well as to the development of various animal forms and particularly of man himself. The author's concluding words can be advantageously quoted here:

"Mankind during an incalculably long and complex evolutionary process rose from the primeval ooze through an incessant struggle for survival, principally through the instrumentality of vision and light, to the life of selfconsciousness and the realization of the world. Whether it will ever attain the status which would justify its name "Wise Man," [*Homo sapiens*] given to it by Linné, is beyond our knowledge to foretell. To paraphrase Aristotle's words quoted in the Introduction—to foresee the fate of Mankind certainly is one of the most difficult things in the world!

"Turning to the practical side of human affairs, vision, just like life, is a heavenly gift bestowed upon Man for whatever use he is capable of putting it to. With it we are able to see and appreciate and understand countless objects necessary in our daily life and make use of them in many practical ways.

"But vision has also higher, spiritual attributes capable of elevating human beings above the level of mere brutes struggling for existence. Vision makes us see and appreciate the smile on a friendly face, enjoy the endless beauties of nature, the multicolored flowers, birds, and fruits, the green meadows and somber deserts, the glorious sunrise and sunset, the majesty of the tall mountains and the sweeping horizon of the ocean, the magnificence of an Alhambra and of a Taj Mahal, and all other things which make our visible world.

"Through sight we judge our fellow-men and are principally guided in the choice of our friends and sexual mates. Through sight, we appreciate the innumerable works of art and, in civilized societies, receive and preserve most of our knowledge.

"The gateway of vision to the human mind is wide open, the avenue that leads to it is smooth and broad. Man's opportunity given to him by nature is great."

This review cannot be completed without a brief word regarding the handiwork of Heinrich Klüver, without which this classic would not have been possible. Ironically seriously failing vision dogged the final years of the life of Stephen Polyak and on March 9, 1955 inadequate coronary vessels, which disability had been evident before, took his life. Foreseeing his approaching disability, Polyak received from Klüver his promise to see this book through to publication. This generous promise cost this outstanding experimental psychologist two years of his scientific life. I believe that all will agree with me that his efforts have been worth while.

Quite apart from this book's outstanding scientific merits, is the language in which it is written. Above are quoted two selections. It makes anyone, whose native language is English, most humble to see this man born in Yugoslavia, educated in Croatian and German, handle this adopted language so masterfully. Doubtless his devoted wife, Donna Polyak, is in considerable measure responsible for this. Nonetheless this is an outstanding accomplishment. This use of clear English to express himself unambiguously is both delightful and remarkable, particularly to one across whose editorial desk numerous examples of the tortured and misused English language pass day after day.

The University of Chicago Press is to be congratulated on having produced an excellent volume. The illustrations are well reproduced. The choice of the typeface has been a fortunate one and the printing and proofreading have been excellent. The fact that this valuable book, which is unlikely to be a financial success, has been produced is a tribute to the good judgment of the administrators of the several funds that have supported it.

Lastly, note must be taken of a most extensive and complete bibliography of three hundred pages and 10,000 entries, and of a thorough index of thirty-two pages.

PAUL C. BUCY, M.D.

NOTICES

AMERICAN BOARD OF NEUROLOGICAL SURGERY

The American Board of Neurological Surgery had its 37th official meeting in New Haven, Connecticut, Nov. 3–6, 1957. At the spring meeting of the Board there had been considerable discussion regarding the preliminary surgical training before beginning the neurosurgical residency. It was pointed out at that time that a number of states require a rotating internship as a prerequisite to admission to practice in that state, and this, in effect, worked a hardship on candidates who wished to reside in those states, because it required an additional six months of general surgical training. Since it had been the original intent of the Board that the training program in neurological surgery should be five years beyond graduation, this brought about certain inequities. At this Board session, therefore, the By-laws were changed so that an individual may now enter a neurosurgical residency after he has completed either a straight surgical internship or a rotating internship. If he has completed at least one year of general surgery, then he must have four years of approved neurosurgical residency training which must include at least thirty months of clinical neurological surgery. The other eighteen months may be spent as the candidate and the chief of the service see fit, but it may embrace additional training in neurological surgery, general surgery, neurology, the basic sciences, or in experimental work. In any event, the candidate must be prepared to pass the Board examinations in organic neurology, neuropathology, neuroanatomy, x-ray diagnosis, neurological surgery and general surgery.

If a candidate has had a rotating internship, then he may begin a neurosurgical residency, which again must include thirty months of clinical neurological surgery but in addition must include six months of general surgical training in an approved surgical residency training program. This individual, therefore, would have only twelve months of time which may be devoted to either additional neurological surgery, to organic neurology, to the basic sciences, work in the laboratory, etc., but he must also be prepared to pass the examinations in the basic sciences.

These periods of training are, of course, only the minimum suggested by the Board, and individual training programs may still be longer if the chief of the service and the trainee so desire.

A candidate may begin his residency in neurological surgery after a rotating internship on or after Jan. 1, 1958.

The By-laws were also changed so that the fee for certification shall be from now on $150.00, instead of $100.00. The fee of $100.00 was set originally in 1940 and has not been advanced. However, it is becoming increasingly obvious that the rising costs of food, transportation, hotel accommodations, etc. will necessitate an increase in the certification fee. The members of the Board serve without any remuneration, only their expenses being paid to, from, and during the Board examinations. Associate examiners are paid a per diem rate, plus expenses when indicated. A moderate secretarial allowance is the only fixed monthly item of expense. It was therefore agreed that the application fee should remain at $25.00, but that this fee should not be returned even though the application is denied. This practice has been in effect for a number of years. In addition, a charge of $125.00 will be made

for the examination fee. If a candidate fails and has to repeat the examination, either in part or in toto, a re-examination fee of $50.00 will then be charged.

Examinations were given by the American Board of Neurological Surgery in New Haven, Connecticut, Nov. 4–6, 1957, and the following were certified:

ALLEN, LEROY 309 Woodburn, Raleigh, N. C.
ANDERSON, ROBERT K. 715 Lake St., Oak Park, Ill.
ANGELO, MARTIN A. 591 Delaware Ave., Buffalo 2, N. Y.
BAISAS, ROGER C. (Foreign) Pinamalayan, Oriental Mindoro, Philippines
BOTTERELL, E. HARRY 280 Bloor St., West, Toronto 5, Ontario, Can.
COWLEY, HOWARD S. 1720 Springhill Ave., Mobile, Ala.
DUGGER, GORDON S. University of North Carolina School of Medicine, Chapel Hill, N. C.
FAULK, MURL E., JR. 675 Fifth St., Beaumont, Texas
FRANKEL, SAUL A. Yale University School of Medicine, 333 Cedar St., New Haven 11, Conn.
GRAY, GEORGE H., JR. Mercy Hospital, Pittsburgh 19, Pa.
GUSTAFSON, MAYNARD B. 702 1st Ave., South, Fargo, N. D.
HANNA, DUKE E. 652 Howland Dr., Inglewood, Calif.
JAEGER, ROBERT M. 1746 Allen St., Allentown, Pa.
KAUFMAN, ALBERT A. 4120 Atlantic Ave., Long Beach, Calif.
LEVY, RICHARD W. 1322 Aline St., New Orleans, La.
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MELOCHE, BERNARD R. 1150 East Blvd., St. Joseph, Montreal 34, Quebec, Can.
MULLAN, JOHN F. Dept. of Neurological Surgery, University of Chicago, Chicago 37, Ill
OGLE, WILLIAM S. 22 North Manassas St., Memphis, Tenn.
PAPPAS, GEORGE N. 62 South Highland Ave., Ossining, N. Y.
PIERCE, MICHAEL A. 70 Park St., Montclair, N. J.
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SHOEMAKER, HENRY K. Jefferson Medical College Hospital, 10th & Sansom, Philadelphia, Pa.
SUTHERLAND, DANIEL L. 24 Queens Road, St. John's, Newfoundland, Can.
TSURU, MITSUO (Foreign) c/o Surgical Dept., School of Medicine, Hokkaido University, Sapporo, Japan
WANNAMAKER, GORDON T. Tripler U. S. Army Hospital, Honolulu, Hawaii
WILLIAMS, JAMES R. Kennedy V. A. Hospital, Memphis 15, Tenn.
WITT, JOSEPH A. U. S. Navy
WU, WILLIAM Q. 701 East 63rd St., Kansas City, Mo.

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY

The winner of the Third Annual American Academy of Neurological Surgery Award is Dr. Byron C. Pevehouse, University of California Hospitals, San Francisco, California, who submitted the paper entitled "Observations on Methods of Induced Hypotension and Hypothermia in the Rhesus Monkey."

The Academy announces its Fourth Annual Award. This is intended as an incentive to research by younger neurosurgeons during or immediately following their formal training. It is given for the best paper submitted reporting original clinical or laboratory research pertaining to the nervous system for which the author has had the primary responsibility. The paper shall not have been accepted for publication in any journal but may have been submitted as a thesis for a degree. When subsequently published, it shall carry the footnote "American Academy of Neurological Surgery Award, 1958."

Eligibility is confined to doctors of medicine currently in training in neurological surgery or to those who have completed their training since June 30, 1956. Those certified by the American Board of Neurological Surgery or the Royal College of

Surgeons of Canada, subspecialty neurosurgery, or have other equivalent certifications, are not eligible.

The recipient of the Award will present his paper at the 20th Annual Meeting of the American Academy of Neurological Surgery at the Royal York Hotel, Toronto, Canada, November 6–8, 1958. His expenses while attending the meeting and his travel expenses to and from his home (if living outside the North American Continent, from the port of entry into the United States) will be borne by the Academy. In addition, there will be an honorarium of one hundred dollars.

Manuscripts to be considered by the Award Committee should be sent to Dr. Eben Alexander, Jr., Secretary of the Academy, at the Bowman Gray School of Medicine, Winston-Salem, North Carolina, and should be submitted before July 15, 1958. A résumé of the candidate's postdoctoral training must accompany the paper when submitted.

ELDRIDGE H. CAMPBELL MEMORIAL SURGICAL RESEARCH LABORATORY

The dedication ceremony of the Eldridge H. Campbell Memorial Surgical Research Laboratory was held at the Albany Medical College on December 6, 1957. Mr. James F. Adams, President, the Board of Trustees, and Dr. Charles Eckert, Chairman, Department of Surgery, spoke on behalf of the Albany Medical College. An address was delivered by Dr. Frank B. Berry, Assistant Secretary of Defense. Dr. Harold C. Wiggers, Dean, officiated at the unveiling of a memorial plaque.

MEETINGS

Academy of Neurosurgery of San Diego, San Diego, Calif., January 1958. Dr. Robert C. Greenwood, 233 A St., San Diego 1, Calif., Secretary.

American Academy of Neurological Surgery, Royal York Hotel, Toronto, Canada, November 6–8, 1958. Dr. Eben Alexander, Jr., Bowman Gray School of Medicine, Winston-Salem, N. C., Secretary.

American Neurological Association, Claridge Hotel, Atlantic City, New Jersey, June 16–18, 1958. Dr. Charles Rupp, 133 South 36th St., Philadelphia 4, Pa., Secretary.

Harvey Cushing Society, Mayflower Hotel, Washington, D. C., April 21–23, 1958. Dr. David L. Reeves, 316 West Junipero St., Santa Barbara, Calif., Secretary.

Interurban Neurosurgical Society, Athletic Club, Columbus, Ohio, February 8, 1958. Dr. Harry F. LeFever, 1275 Olentangy River Road, Columbus 8, Ohio.

Neurosurgical Society of America, Key Biscayne, Florida, January 15–18, 1958. Dr. Frank P. Smith, 260 Crittenden Blvd., Rochester 20, N. Y., Secretary.

New York Society of Neurosurgery, New York Academy of Medicine Bldg., New York City, January 21, 1958. Dr. Henry Wigderson, 162-05 89th Ave., Jamaica 32, N. Y., Secretary.

Society of British Neurological Surgeons, Wassenaar and Utrecht, Holland, May 8–10, 1958. Mr. D. W. C. Northfield, London Hospital, London E.1., England, Secretary.

Southern California Neurosurgical Society, Del Monte Lodge, Del Monte, Calif., February 28–March 2, 1958 (in conjunction with the San Francisco Neurological Society). Dr. Robert H. Pudenz 744 Fairmount Ave., Pasadena, Calif., Secretary.

JOURNAL OF NEUROSURGERY

The *Journal of Neurosurgery* is devoted to the publication of work relating primarily to neurosurgery, including studies in clinical neurophysiology, organic neurology, ophthalmology, radiology and pathology. Short articles on unusual cases and on technique, special instruments or equipment that might be useful to others in the field are also acceptable.

MANUSCRIPTS are accepted with the understanding that they are contributed solely for publication in this *Journal*. They should be addressed to Dr. Louise Eisenhardt, 333 Cedar Street, New Haven 11, Connecticut, U.S.A. They should be typewritten in double space, with tabular matter and passages for small print on separate sheets. All materials should be mailed flat.

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Articles: Name of author, full title of article, name of periodical, year, volume, first and last page of article. Abbreviations of names of periodicals should conform to the style used in *World list of scientific periodicals published in the years 1900–1950* (London: Butterworths Scientific Publications, 1952).

Books: Name of author, full title of book, city, publisher, year, edition, full pagination (if book is in more than one volume, give the number of volumes).

ILLUSTRATIONS. Care should be taken not to use too many illustrations. All figures approved by the Editorial Board are provided free of charge with the exception of color plates which are inserted at the expense of the contributor. Permission must be obtained from the subject for reproduction of identifiable photographs of patients. If illustrations are larger than 8.5×11 inches, reduced glossy prints should be submitted instead. Any lettering should be large enough to permit necessary reduction. Paper clips should not be used on prints. A hard pencil should not be used in writing on the back of prints. Illustrations should be numbered and the top plainly indicated. Illustrations should be submitted UNMOUNTED.

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CONTENTS

1. In Favor of Simplicity: Applied to Medicine in General and Neurosurgery in Particular. R. EUSTACE SEMMES 1

2. Hypothermia in the Surgical Treatment of Ruptured Intracranial Aneurysms. E. H. BOTTERELL, W. M. LOUGHEED, T. P. MORLEY and S. L. VANDEWATER 4

3. Retinal Artery Blood Pressure Measurements in Diagnosis and Surgery of Spontaneous Carotid Occlusions. MAURICE W. VAN ALLEN, FREDERICK C. BLODI, and EDGAR S. BRINTNALL 19

4. Evaluation of Roentgen Contrast Agents Used in Cerebral Arteriography. I. A Simple Screening Method. G. MARGOLIS, G. T. TINDALL, R. L. PHILLIPS, P. D. KENAN, and K. S. GRIMSON .. 30

5. Evaluation of Roentgen Contrast Agents Used in Cerebral Arteriography. II. Application of a New Method. G. T. TINDALL, P. D. KENAN, R. L. PHILLIPS, G. MARGOLIS, and K. S. GRIMSON 37

6. Lactic Dehydrogenase of Cerebrospinal Fluid in the Differential Diagnosis of Cerebrovascular Disease and Brain Tumor. RUTH KERR JAKOBY, and WILLIAM B. JAKOBY 45

7. Mechanism and Control of Centrally Induced Cardiac Irregularities During Hypothermia. Part I. Clinical Observations. J. LAWRENCE POOL, and LAIBE A. KESSLER 52

8. The Pathology of Supratentorial Angiomas. WALLACE B. HAMBY 65

9. Localization of Brain Tumors at Operation with Radioactive Phosphorus. An Improved Technique Using a Proportional Counter. CHARLES V. ROBINSON, and BERTRAM SELVERSTONE 76

10. Arteriovenous Aneurysms of the Spinal Cord. A Report of Two Cases Investigated by Vertebral Angiography. OLLE HÖÖK, and HANS LIDVALL 84

11. The Prevention of Experimental Contrast Medium Injury to the Nervous System. P. D. KENAN, G. T. TINDALL, G. MARGOLIS, and R. S. WOOD 92

EDITORIAL 96

SPECIAL ARTICLE:

The Reticular Formation. J. D. FRENCH 97

CASE REPORT:

Spinal Lithiasis. A Case Report. WILLIAM H. FAETH 116

BOOK REVIEW 120

NOTICES 122

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